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(54) PROCESS FOR PREPARING 1,2,3,4-TETRAHYDROISOQUINOLINES

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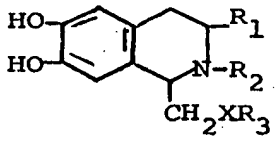
The present invention relates to new 1,2,3,4-tetrahydroisoquinolines having relaxing activity on smooth muscles and their process of preparation.

According to one aspect of the invention there is provided new 1,2,3,4-tetrahydroisoquinolines having the general formula:



[I]

wherein R_1 and R_2 are each hydrogen or lower alkyl group, X is oxygen or sulfur, and R_3 is phenyl group having 1 to 3 substituents selected from the group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, mono or di(lower)alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy, phenyl(lower)alkoxy which may be substituted with lower alkyl and phenyl which may be substituted with lower alkyl, and the pharmaceutically acceptable acid addition salts thereof.

It is to be understood that the term "lower alkyl" and "lower alkoxy" where used herein denote groups having 1 to 6 carbon atoms, "lower alkylenedioxy" denotes group having 1 to 3 carbon atoms and "halogen" denotes chlorine, bromine, fluorine or iodine atom unless otherwise indicated.

The suitable example of lower alkyl group may be a lower alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or hexyl, and preferably a lower alkyl group having 1 to 4 carbon atoms, and more preferably a lower alkyl group having 1 to 2 carbon atoms.

The suitable example of lower alkoxy group may be

a lower alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, isopentoxy or hexyloxy, and preferably a lower alkoxy group having 1 to 4 carbon atoms, and more preferably a lower alkoxy group having 1 to 2 carbon atoms.

The suitable example of halo(lower)alkyl group may by a halo(lower)alkyl group having 1 to 6 carbon atoms, such as chloromethyl, fluoroethyl, chloropropyl, bromopropyl, iodobutyl, chloropentyl, bromochloroethyl, dichloromethyl, dichloroethyl, dibromomethyl, dibromoethyl, difluoromethyl, dichloropropyl, dichlorobutyl, dibromopropyl, difluoropropyl, trichloromethyl, tribromomethyl, trifluoromethyl, trichloroethyl or tribromoethyl, and preferably a halo(lower)alkyl group having 1 to 4 carbon atoms, and more preferably a halo(lower)alkyl group having 1 to 2 carbon atoms.

The suitable example of lower alkylenedioxy group may be a lower alkylenedioxy group having 1 to 3 carbon atoms, such as methylenedioxy, dimethylmethylenedioxy or ethylenedioxy.

As the suitable mono or disubstituted amino group, there may be, for example, mono or di(lower)alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino, methylethylamino, or dipropylamino), an acylamino (e.g. acetylamino, propionylamino, isopropionylamino, benzoylamino, toluylamino, benzylcarbonylamino, p-chlorobenzoylamino, o-nitrobenzoylamino, or m-methoxybenzoylamino), an arylamino (e.g. phenylamino, o-nitrophenylamino, m-nitrophenylamino, or p-nitrophenylamino), an aralkylamino (e.g. benzylamino, or p-bromobenzylamino), and an alkane or benzenesulfonylamino (e.g. methanesulfonylamino, ethanesulfonyl-

amino, benzenesulfonylamino, toluenesulfonylamino, or p-methoxybenzenesulfonylamino).

As the suitable aryloxy group, there may be, for example, phenoxy, tolyloxy, and xylyloxy.

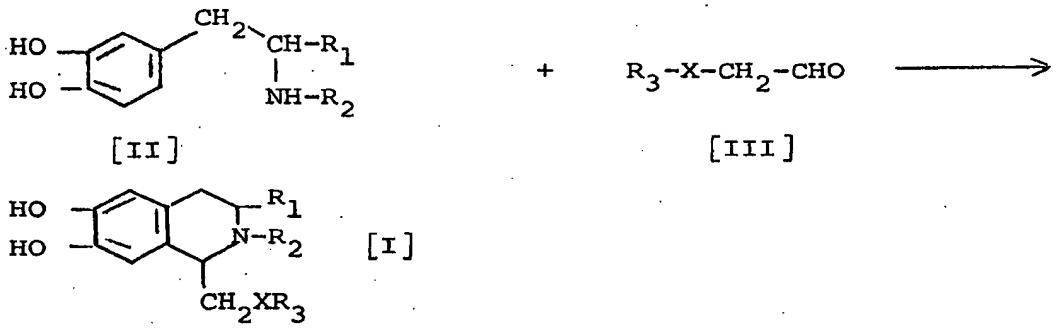
As the suitable acyloxy group, there may be, for example, an alkanoyloxy (e.g. acetoxy, propionyloxy, isopropionyloxy, or butyryloxy) and an aroyloxy (e.g. benzoyloxy, toluyloxy, p-chlorobenzoyloxy, nitrobenzoyloxy, or o-methyloxybenzoyloxy), an aryloxy(or thio)carbonyloxy (e.g. phenoxycarbonyloxy, or phenylthiocarbonyloxy), and an aralkanoyloxy (e.g. benzylcarbonyloxy).

As the suitable aralkyloxy group, there may be, for example, benzyloxy, tolylmethyloxy and xylylmethyloxy. And as the suitable aryl group, there may be, for example, phenyl, tolyl and xylyl.

The present 1,2,3,4-tetrahydroisoquinolines of the formula [I] and the pharmaceutically acceptable salts thereof have relaxing activity on smooth muscles, especially on vascular-smooth and viseral-smooth muscles. Accordingly, they show vasodilating, intestinal-contraction inhibiting and bladder-contraction inhibiting activities, not showing bronchodilating activity, and are useful as vosodilating, intestinal contraction inhibiting and bladder-contraction inhibiting agents.

According to the present invention, the 1,2,3,4-tetrahydroisoquinolines of the formula [I] can be prepared by various methods as mentioned hereinunder.

One process is illustrated by the following reaction scheme:



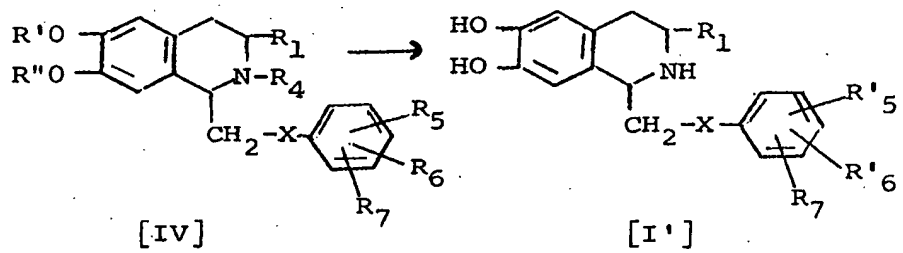
[II] + [III] ⟶ [I]

wherein R_1 and R_2 are each hydrogen or lower alkyl group, X is oxygen or sulfur, and R_3 is phenyl group having 1 to 3 substituents selected from the group consisting of lower alkylenedioxy, phenyl(lower)alkoxy which may be substituted with lower alkyl, phenoxy which may be substituted with lower alkyl, phenyl which may be substituted with lower alkyl, mono- or di(lower)-alkyl amino or alkanesulfonamido.

The reaction is effected by reacting a 3,4-dihydroxyphenethylamine derivative of the formula [II] or its salt with an acetaldehyde derivative of the formula [III] or its acetal, hemiacetal or hydrate to give the desired, novel 1,2,3,4-tetrahydroisoquinoline derivative [I] or its salt. Among the starting 3,4-dihydroxyphenethylamine derivatives [II], 3,4-dihydroxyphenethylamine can be prepared, for instance, by the method described in Chemical Abstracts, Vol. 45 (1951), column 1970d, and the other starting compounds can be also prepared by the method similar to that described in said journal or other methods known in the arts. As the salt of the starting compounds [II], there may be a salt with an inorganic acid (e.g. hydrochloric acid, sulfuric acid, or hydrobromic acid) or an organic acid (e.g. acetic acid, picric acid, oxalic acid, or tartaric acid). The present reaction is preferably carried out in the presence of an acid, such as hydrochloric acid, sulfuric acid, hydrobromic acid, acetic

acid, propionic acid, picric acid or the like, without solvent or in a solvent, such as methanol, ethanol, benzene, chloroform, dioxane or other organic solvent inert to the reaction. There is no limitation to the reaction temperature, and it can be carried out at room temperature to an elevated temperature, but preferably with heating.

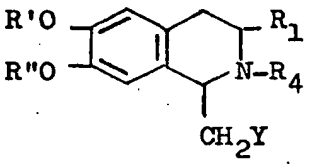
One of the alternative processes can be illustrated by the following reaction scheme:



[IV] [I']

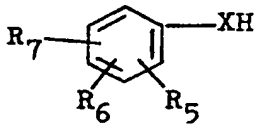
wherein R_1 is hydrogen or lower alkyl group, R' and R" are hydrogen or a protecting group of hydroxy group, R_4 is a protecting group of imino group, R_5 is hydroxy, protected hydroxy, amino, protected amino, mono or di(lower)alkylamino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl group, or phenyl which may be substituted with lower alkyl, R_6 is hydrogen, hydroxy, protected hydroxy, amino, protected amino, lower alkoxy group or halogen, R_7 is hydrogen or lower alkoxy group, R'_5 is hydroxy, amino, mono or di(lower)alkylamino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl group, or phenyl which may be substituted with lower alkyl, R'_6 is hydrogen, hydroxy, amino, lower alkoxy group or halogen, and X is oxygen or sulfur.

The starting 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivatives [IV], which are novel compounds, can be prepared by reacting a compound of the formula:



[V]

wherein R_1, R_4, R' and R" are the same as defined above, and Y is halogen, with a compound of the formula:



[VI]

wherein R_5, R_6, R_7 and X are the same as defined above.

In the above compounds [IV], [V] and [VI], as the suitable individual protecting group of a hydroxy group, there are inclusive all the conventional protecting groups of hydroxy group, and may be, for instance, an easily removable acyl group, such as acetyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 4-(4-methoxyphenylazo)benzyloxycarbonyl, t-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 3-iodopropoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, 1-cyclopropylethoxycarbonyl, 8-quinolyloxycarbonyl and trifluoroacetyl, and further benzyl, trityl, methoxymethyl, 2-nitrophenylthio, tetrahydropyranyl, 2,4-dinitrophenylthio, and the like. As the suitable protecting group of the hydroxy groups of R' and R", there may be, for instance, an alkylene group, such as methylene, ethylene and dimethylmethylene, which are formed when R' and R" are bound together.

As the suitable protecting group of amino and imino groups, there are inclusive all conventional protecting groups of amino and/or imino groups, and may be, for instance, an easily removable acyl group, such as trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, p-toluenesulfonyl, p-nitrobenzyloxycarbonyl, o-bromobenzyloxycarbonyl, o-nitrophenylsulfenyl, acetyl, chloroacetyl, trifluoroacetyl, formyl, t-butoxycarbonyl, p-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 4-(4-methoxyphenylazo)benzyloxycarbonyl, pyridine-1-oxide-2-methoxycarbonyl, 2-pyridylmethoxycarbonyl, 2-furyloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, 1-cyclopropylethoxycarbonyl, 1-adamantyloxycarbonyl and 8-quinolyloxycarbonyl group, and other easily removable protecting group, such as trityl, 2-nitrophenylthio, 2,4-dinitrophenylthio, 2-hydroxybenzylidene, benzylidene, 4-nitrobenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthylmethylene, 3-hydroxy-4-pyridylmethylene, 1-methoxycarbonyl-2-propylidene, 1-ethoxycarbonyl-2-propylidene, 3-ethoxycarbonyl-2-butylidene, 1-acetyl-2-propylidene, 1-benzoyl-2-propylidene, 1-[N-(2-methoxyphenyl)carbamoyl]-2-propylidene, 1-[N-(4-methoxyphenyl)carbamoyl]-2-propylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acethylcyclohexylidene, 3,3-dimethyl-5-oxocyclohexylidene, and di or trialkylsilyl group.

The reaction which is illustrated by the above reaction scheme is effected by subjecting a 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivative of the formula [IV] to a reaction for removing the protecting groups

to give the desired, novel 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivative [I'] or its salt. The reaction for removing the protecting groups can be carried out by conventional methods Known in the art, for instance by hydrolysis with an acid or an alkali or by catalytic reduction, in accordance with the kinds of the protecting groups.

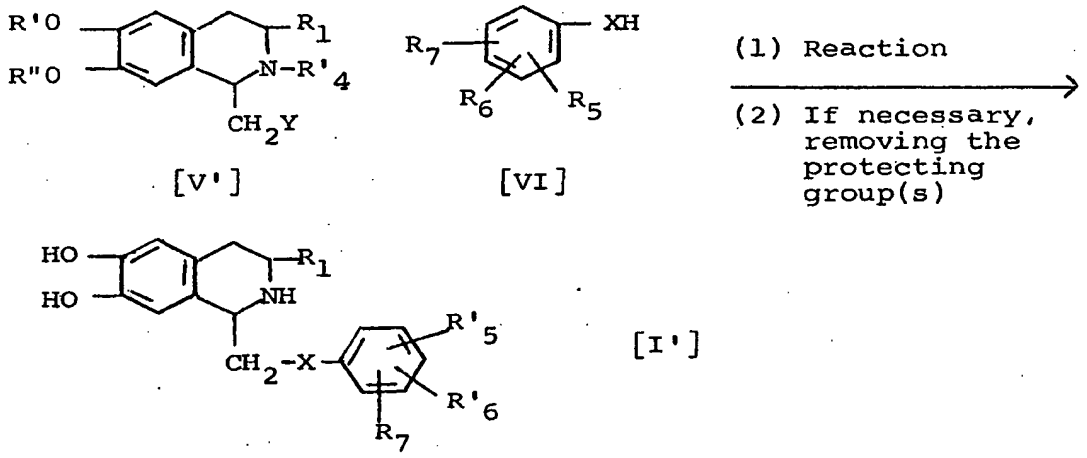
Among the conventional methods, the hydrolysis with an acid is one of the most convenient methods and is applied to in the case of such protecting groups as benzyloxycarbonyl, substituted benzyloxycarbonyl, alkoxycarbonyl, substituted alkoxycarbonyl, adamantyloxycarbonyl, toluenesulfonyl, trityl, methoxymethyl, substituted phenylthio, and lower alkylene which is formed by binding together R' and R". The most suitable examples of the acid used in the hydrolysis may be hydrobromic acid, hydrochloric acid, formic acid, acetic acid, trifluoroacetic acid, and the like which can be easily distilled off from the reaction system at a reduced pressure. The hydrolysis can be carried out without solvent or in an appropriate solvent, such as hydrophilic organic solvent, water or a mixed solvent thereof.

The catalytic reduction may be applied to in case of the protecting groups, such as benzyloxycarbonyl, substituted benzyloxycarbonyl, 2-pyridylmethoxycarbonyl, diphenylmethoxycarbonyl, benzyl or trityl. The most convenient catalyst is palladium catalyst but other catalysts can be also employed. In the reduction reaction, when R_5 is nitro group, it is also reduced into amino group, but it should be understood that the reduction accompanied with such side reaction also falls within the scope of the present invention.

It is to be understood that the other conventional

methods for removing protecting groups may be also employed. For instance, trifluoroacetyl group can be removed by treating the trifluoroacetyl-protected compound with water, halogen-substituted alkoxycarbonyl and 8-quinolyloxycarbonyl can be removed by treating the protected compound with a heavy metal such as copper or zinc, and further methanesulfonyl, toluenesulfonyl or the like can be removed by treating the protected compound with metal sodium in liquid ammonia.

Another alternative process is illustrated by the following reaction scheme:



wherein R_1 is hydrogen or lower alkyl group, R' and R" are hydrogen or a protecting group of hydroxy group, R'_4 is hydrogen or a protecting group of imino group, R_5 is hydroxy, protected hydroxy, amino, protected amino, mono or di(lower)alkylamino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl group, or phenyl which may be substituted by lower alkyl, R_6 is hydrogen, hydroxy, protected hydroxy, amino, protected amino, lower alkoxy group or halogen, R_7 is hydrogen or lower alkoxy group, R'_5 is hydroxy, amino, mono or di(lower)alkylamino, lower

alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl group, or phenyl which may be substituted by lower alkyl, R'_6 is hydrogen, hydroxy, amino, lower alkoxy group or halogen, X is oxygen or sulfur, and Y is a residue of an acid.

The starting compounds of the formula [V'], which are novel compounds, can be prepared, for instance, by reacting 4-(2-aminoethyl)catechol or its derivative with a corresponding substituted acetic chloride and condensing the resultant in the presence of phosphorus oxychloride and then reducing the resultant.

In the above compounds [V'] and [VI], as the suitable individual protecting group of a hydroxy group, there are inclusive all the conventional protecting groups of hydroxy group as mentioned hereinbefore, and as the suitable protecting group of amino and imino groups, there are inclusive all conventional protecting groups of amino and/or imino groups as mentioned hereinbefore. As the suitable residue of an acid defined for Y, there may be, for instance, a residue of an acid, such as hydrochloric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, alkylsulfuric acid, toluenesulfonic acid, benzenesulfonic acid, and dialkylcarbamic acid.

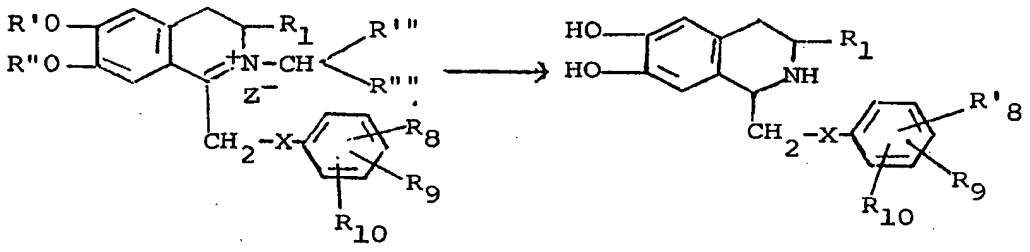
The reaction which is illustrated by the above reaction scheme is effected by reacting a compound of the formula [V'] or its salt with a benzene derivative of the formula [VI], and if necessary, subjecting the resulting compound to a reaction for removing the protecting group(s) to give the desired, novel 1,2,3,4-tetrahydroisoquinoline derivative [I'] or its salt. The suitable salt of the

compound [V'] may be an inorganic acid salt such as hydrochloride, hydrobromide and sulfate, or an organic acid salt such as maleate and lactate.

The reaction of the compound [V'] or its salt with the compound [VI] may be preferably carried out in the presence of a base, such as an alkali or alkaline earth metal (e.g. sodium, potassium, magnesium, or calcium) or its hydroxide, alkoxide, (e.g. ethoxide, propoxide, or t-butoxide), carbonate or bicarbonate, or a strong organic base (e.g. pyridine), and it can be carried out without solvent or in an appropriate solvent, such as a lower alcohol (e.g. methanol or ethanol), ether, benzene, acetone, dioxane, acetonitrile, chloroform, ethylene chloride, tetrahydrofuran, ethyl acetate, or pyridine, or other conventional solvent which is inert to the reaction. There is no limitation to the reaction temperature, and it can be carried out at any temperature from room temperature to an elevated temperature.

The compound thus obtained is optionally subjected to a reaction for removing the protecting group(s). The reaction for removing the protecting groups can be carried out by conventional methods known in the art, for instance by hydrolysis with an acid or an alkali or by catalytic reduction, in accordance with the kinds of the protecting groups. The hydrolysis and catalytic reduction can be carried out in the same manner as described hereinbefore in case of the reaction for removing the protecting groups of the 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivatives [IV].

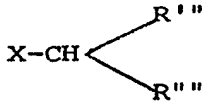
A further alternative process can be illustrated by the following reaction scheme:



[VII] [I"]

wherein R_1 is hydrogen or lower alkyl group, R' and R" are hydrogen or a protecting group of hydroxy group, R'" is hydrogen or lower alkyl group, R"" is phenyl or lower alkoxy group, R_8 is hydroxy, lower alkoxy, nitro, amino, mono or di(lower)alkylamino, phenoxy, halogen, halo(lower)alkyl group, or phenyl which may be substituted with lower alkyl, R_9 is hydrogen, hydroxy, lower alkoxy group or halogen, R_{10} is hydrogen or lower alkoxy group, R'_8 is hydroxy, lower alkoxy, amino, mono or di(lower)alkylamino, phenoxy, halogen, halo(lower)-alkyl group, or phenyl which may be substituted with lower alkyl, X is oxygen or sulfur, and Z is a residue of an acid, for example, hydrochloric acid, sulfuric acid, hydrobromic acid, benzenesulfonic acid and di(lower)alkylcarbamic acid.

The starting immonium compounds of the formula [VII], which are novel compounds, can be prepared, for instance by reacting 4-(2-aminoethyl)catechol or its derivative with a corresponding substituted acetic chloride, condensing the resultant in the presence of phosphorus oxychloride and then reacting the resultant with a compound of the formula:



[VIII]

wherein R'", R"" and Z are the same as defined above.

In the above compound [VII], as the suitable individual protecting group of a hydroxy group, there are inclusive all the conventional protecting groups of hydroxy group as mentioned hereinbefore.

The reaction which is illustrated by the above reaction scheme is effected by reducing stepwise or at once an immonium compound of the formula [VII] to give the desired, novel 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivative [I"] or its salt.

As the reduction methods, there may be a reduction with an alkali metal borohydride (e.g. lithium borohydride, sodium borohydride, or potassium borohydride), an alkaline earth metal borohydride (e.g. calcium borohydride, magnesium borohydride, or barium borohydride), an alkali metal aluminum hydride (e.g. lithium aluminum hydride, sodium aluminum hydride, or potassium aluminum hydride) or a metal and an acid [e.g. an metal such as iron, zinc or tin and an acid such as an inorganic acid (hydrochloric acid, sulfuric acid, or the like) or an organic acid (acetic acid or the like)], or a catalytic reduction by using platinum oxide, palladium-carbon, Raney nickel or the like as the catalyst. Among the reduction methods, when the immonium compound [VII] is reduced with an alkali metal borohydride, an alkaline earth metal borohydride, or an alkali metal aluminum hydride, the reduction is proceeded stepwise (i.e. partially), and therefore, the resultant should be subjected to a further reduction with other reducing agent.

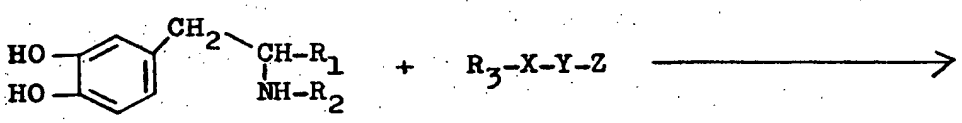
The reaction conditions such as solvent and reaction temperature should be decided in accordance with the used reduction method. For instance, when an alkaline earth

metal borohydride is used, the reaction is carried out by a conventional method. i.e. in an inert solvent such as water, methanol, ethanol, tetrahydrofuran or dioxane at room temperature or at an elevated temperature. When water is used as the solvent, it is preferable to add a small amount of alkali for stabilizing the reagents, and when other solvent is used, there may be added an alkali likewise.

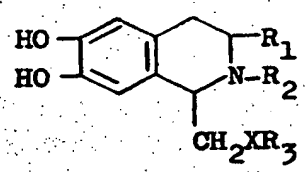
When an alkali metal aluminum hydride is used, the reaction is carried out also by a conventional method, i.e. in essentially anhydrous, inert solvent such as diethyl ether, dibutyl ether, tetrahydrofuran or dioxane at room temperature or at an elevated temperature.

The reduction with a metal and an acid or the catalytic reduction is also carried out by conventional methods. The catalytic reduction can be also under a pressure. In the reduction reaction by using a reducing agent other than alkali metal borohydride, when R_8 is nitro group, it is also reduced into amino group, but it should be understood that the reduction accompanied with such side reaction also falls within the scope of the present invention.

Still further alternative process can be illustrated by the following reaction scheme:



[II] [IX]



[I]

wherein R_1 and R_2 are each hydrogen or lower alkyl group, R_3 is phenyl group having 1 to 3 substituents selected from the group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, mono or di(lower)alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy group, phenoxy which may be substituted by lower alkyl, phenyl(lower alkoxy) which may be substituted with lower alkyl, X is oxygen or sulfur, Y is formylmethylene or a group convertible thereto under an acidic condition, and Z is carboxy group or its derivative.

In the above compound [IX], as the group convertible into formylmethylene under an acidic condition defined for Y, there may be, for instance, a group which the formyl moiety is in a form of acetal, hemiacetal, hydrate (diol), mono or diacylated diol, thioacetal, hemithioacetal, Schiff's base, oxime, semicarbazone, thiosemicarbazone or the like; an acyloxyvinyl group (e.g. acetoxyvinyl or propionyloxyvinyl); a lower alkoxyvinyl group (e.g. methoxyvinyl, ethoxyvinyl, propoxyvinyl, or isopropoxyvinyl); a lower alkylthiovinyl group (e.g. methylthiovinyl, ethylthiovinyl, or propylthiovinyl); or aminovinyl group, but it is not limited thereto and is inclusive any other group convertible into formylmethylene under the reaction condition of the present method.

As the derivative at the carboxy group defined for Z, there may be, for instance, the groups defined as follows:

(a) Esters:

There may be inclusive all active esters or inactive esters. For instance, the ester moiety may be a saturated or unsaturated, cyclic or acyclic alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclohexyl, cycloheptyl, vinyl, 1-propenyl, 2-propenyl, or 3-butenyl); an aryl (e.g. phenyl, xylyl, tolyl, or naphthyl); an aralkyl (e.g. benzyl

or phenethyl); a group which the carbon atom of the above alkyl or aralkyl is replaced by sulfur, nitrogen or oxygen atom or carbonyl group (e.g. methoxymethyl, ethoxymethyl, methylthioethyl, methylthiomethyl, dimethylaminoethyl, diethylaminoethyl, phenoxymethyl, phenylthiomethyl, methylsulfenylmethyl, phenylsulfenylmethyl, benzoylmethyl, or tolylmethyl); and a group which the above groups have 1 or more substituents such as cyano, nitro, halogen (e.g. fluorine, chlorine or bromine), lower alkoxy (e.g. methoxy, ethoxy, or propoxy), an alkanesulfonyl and phenylazo, for example, chloromethyl, bromomethyl, trichloroethyl, cyanomethyl, p-nitrophenyl, 2,4,5-trichlorophenyl 2.4,6-trichlorophenyl, pentachlorophenyl, p-methanesulfonylphenyl, 4-(phenylazo)phenyl, 2,4-dinitrophenyl, p-chlorobenzyl, o-nitrobenzyl, p-methoxybenzyl, p-nitrobenzyl, 3,4,5-trimethoxybenzyl, bis(p-methoxyphenyl)methyl, pentachlorobenzyl, trichlorobenzyl, 3,5-di-t-butyl-4-hydroxybenzyl, p-nitrophenylthiomethyl, p-chlorophenylthiomethyl, p-nitrobenzoylmethyl, or p-chlorobenzoylmethyl. And further, there may be inclusive other esters with a substituted or unsubstituted thioalcohol, N-hydroxysuccinimide, N-hydroxyphthalimide, tetrahydropyran, 1-cyclopropylethanol, 1-phenyl-3-methyl-5-pyrazolone, 3-hydroxypyridine, 2-hydroxymethylpyridine-1-oxide, 1-hydroxypiperidine, 1-hydroxy-2(1H)-pyridone, dimethylhydroxylamine, diethylhydroxylamine, glycolamide, 8-hydroxyquinoline, oxime, 2-hydroxymethylquinoline-1-oxide, methoxyacetylene, ethoxyacetylene, t-butylethynyldimethylamine, t-butylethynyldiethylamine, ethylethynyldiethylamine, 2-ethyl-5-(3-sulfophenyl)isoxazolium hydroxide inner salt, and the like.

(b) Amide:

There may be inclusive all acid amides, N-substituted acid amides and N,N-disubstituted acid amides. For instance, there may be a N-lower alkyl acid amide (e.g. N-methyl acid amide, or N-ethyl acid amide); N-phenyl acid amide; a N,N-di(lower alkyl) acid amide (e.g. N,N-dimethyl acid amide, N,N-diethyl acid amide, or N-ethyl-N-methyl acid amide); and other acid amide with imidazole, 4-substituted imidazole or the like.

(c) Acid anhydride:

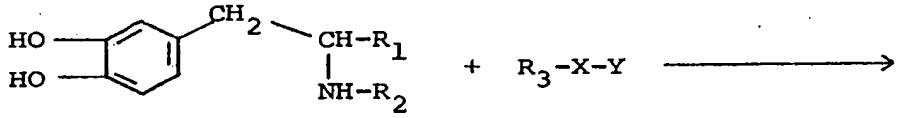
There may be, for instance, a mixed anhydride with dialkylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkylcarbonic acid, an aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutanoic acid, chloroacetic acid, crotonic acid, valeric acid, propionic acid, 3-chloro-2-pentenoic acid, 3-bromo-2-butenoic acid, phenylacetic acid, phenoxyacetic acid, furanacetic acid, or thiopheneacetic acid), or an aromatic carboxylic acid (e.g. benzoic acid); or a symmetrical acid anhydride.

The reaction which is illustrated by the above reaction scheme is effected by reacting 3,4-dihydroxyphenethylamine of the formula [II] or its salt with a malonaldehyde-acid derivative of the formula [IX] to give the desired 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline [I] or its salt.

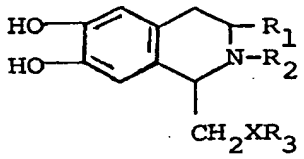
The reaction is carried out in the presence of an acid when the group Y of the starting compound [IX] is a group convertible into formylmethylene group under an acidic condition, and it is carried out usually in the presence of

an acid also when the group Y is formylmethylene group. The suitable examples of the acid may be an inorganic acid such as hydrochloric acid, sulfuric acid or hydrobromic acid, or an organic acid such as acetic acid or propionic acid. Two or more mixtures of these acids can be used. The reaction can be carried out without solvent, but may be done in an appropriate solvent, such as methanol, ethanol, n-butanol, water, chloroform, benzene, dioxane, or other inert solvent. The reaction is carried out at room temperature or at an elevated temperature.

More further alternative process can be illustrated by the following reaction scheme:



[II] [X]



[I]

wherein R_1 and R_2 are each hydrogen or lower alkyl group, R_3 is phenyl group having 1 to 3 substituents selected from the group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, mono or di(lower)alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy group, phenoxy which may be substituted by lower alkyl, phenyl(lower)alkoxy which may be substituted with lower alkyl and phenyl which may be substituted with lower alkyl, X is oxygen or sulfur, and Y is formylmethyl wherein the formyl group is in a form of mono or diacyldiol, thioacetal, hemithioacetal, Schiff's base, oxime, semicarbazone or thiosemicarbazone; (2-acyloxy)vinyl; (2-lower alkoxy)vinyl; (2-lower alkylthio)vinyl or (2-amino)vinyl.

In the compound [X], the suitable examples of the group Y may be (2-hydroxy-2-acetoxy)ethyl, (2-hydroxy-2-propionyloxy)ethyl, (2,2-diacetoxy)ethyl, (2,2-dipropionyloxy)-ethyl, (2,2-dimethylthio)ethyl, (2,2-diethylthio)ethyl, (2-hydroxy-2-methylthio)ethyl, (2-hydroxy-2-ethylthio)ethyl, (2-phenylimino)ethyl, (2-methylimino)ethyl, (2-ethylimino)-ethyl, (2-hydroxyimino)ethyl, (2-carbamoylhydrazino)ethyl, (2-thiocarbamoylhydrazino)ethyl, (2-acetoxy)vinyl, (2-propionyl-oxy)vinyl, (2-methoxy)vinyl, (2-ethoxy)vinyl, (2-propoxy)-vinyl, (2-isopropoxy)vinyl, (2-methylthio)vinyl, (2-ethyl-thio)vinyl, (2-propylthio)vinyl, (2-amino)vinyl, or the like.

The reaction which is illustrated by the above reaction scheme is effected by reacting a 3,4-dihydroxy-phenethylamine of the formula [II] or its salt with a compound of the formula [X] to give the desired 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline [I] or its salt.

The reaction is usually carried out in the presence of an acid, such as an inorganic acid (e.g. hydrochloric acid, sulfuric acid or hydrobromic acid) or an organic acid (e.g. acetic acid or propionic acid), which can be used in a mixture of two or more kinds of them.

The reaction can be carried out without solvent, but may be done in an appropriate solvent. such as methanol, ethanol, n-butanol, water, chloroform, benzene, dioxane, or other inert solvent. The reaction is carried out at room temperature or at an elevated temperature.

The desired compounds of the formula [I], [I'] and [I"] obtained by the above methods may be, if necessary, converted into its salt with an acid, such as an inorganic acid (e.g. hydrochloric acid or sulfuric acid) or an organic

acid (e.g. acetic acid, tartaric acid or picric acid).

The present invention is illustrated by the following examples but not limited thereto.

Example 1

A mixture of 3,4-methylenedioxyphenoxyacetaldehyde diethylacetal (5.1 g), 3,4-dihydroxyphenethylamine hydrochloride (2.7 g), methanol (54 ml), 10 % hydrochloric acid (5 drops) and water (27 ml) was refluxed for 20 hours. The reaction mixture was treated with charcoal and then methanol was distilled off under a reduced pressure. The resulting residue was dissolved in water (50 ml) and washed with chloroform (five times) and ether (once). The aqueous layer was further treated with charcoal and then concentrated. To the resulting residue was added ethanol and benzene, and then water was removed. To the oily substance thus obtained was added acetone. The precipitated crystallines were separated by filtration to give a crude 1-(3,4-methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (4.8 g), M.P. 221° - 223°C.

The crude product was dissolved in a mixture of 95 % ethanol (60 ml) and water (4 ml) and the mixture was treated with charcoal and thereto was added ether. The resulting crystallines were separated by filtration to give a pure product (3.7 g), M.P. 227°C (dec).

Example 2

A mixture of 4-benzyloxyphenoxyacetaldehyde diethylacetal (4.85 g), 3,4-dihydrophenethylamine hydrochloride (9.0 g), methanol (100 ml) and concentrated hydrochloride (1.1 ml) was refluxed under stirring for 18 hours. The reaction was evaporated to dryness under a reduced pressure.

To the resulting residue was added diisopropyl ether. The precipitated crystallines were separated by filtration, recrystallized from methanol-diisopropyl ether to give 1-(4-benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (8.9 g), M.P. 195° - 197°C.

Example 3

A mixture of 4-bisphenylyloxyacetaldehyde diethylacetal (2.4 g), 3,4-dihydroxyphenethylamine hydrochloride (4.1 g), methanol (50 ml), water (25 ml) and concentrated hydrochloric acid (0.5 ml) was refluxed for 18 hours. The reaction mixture was evaporated to dryness under a reduced pressure. The resulting residue was crystallized from 95% ethanol. The crystallines thus obtained were recrystallized from 95% ethanol to give 1-(4-biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 242° - 245°C (dec).

Examples 4 to 6

In the same manner as described in Examples 1 to 3, the following compounds were prepared.

(4) 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 222° - 223.5°C

(5) 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride, NMR spectrum : 6.72 τ (6H, S, $-N(CH_3)_2$), 3.44, 3.45 [each 1H, S, arom-H (5,8)] and 2.40 (4H, S, arom-H).

(6) 1-(3,4-Dimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 229° - 231°C

(6') 1-(4-Methanesulfonamidophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 253° - 255°C.

Example 7

A mixture of 1-(4-chlorophenyl)oxymethyl-2-acetyl-6,7-diacetoxy-1,2,3,4-tetrahydroisoquinoline (450 mg), concentrated hydrochloric acid (10 ml) and 95 % ethanol (15 ml) was refluxed for 16 hours. To the reaction mixture were added water (20 ml) and ethyl acetate (100 ml), and the aqueous layer was taken out and evaporated to dryness under a reduced prossure. The resulting residue was dissolved in isopropyl-alcohol and thereto was added ether. The mixture was allowed to stand. The resulting precipitates were separated by decantation and dried to give 1-(4-chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (150 mg), M.P. 226°C.

Example 8

A mixture of 1-(4-chlorophenyl)oxymethyl-2-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (720 mg), concentrated hydrochloric acid (20 ml) and methanol (100 ml) was refluxed for 16 hours. The reaction mixture was evaporated to dryness under a reduced pressure. The resulting residue was washed with ethyl acetate and chloroform and then dissolved in isopropanol. To the mixture was added ether and the mixture was allowed to stand. The precipitated crystallines were separated by filtration and dried to give 1-(4-chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (420 mg), M.P. 226°C.

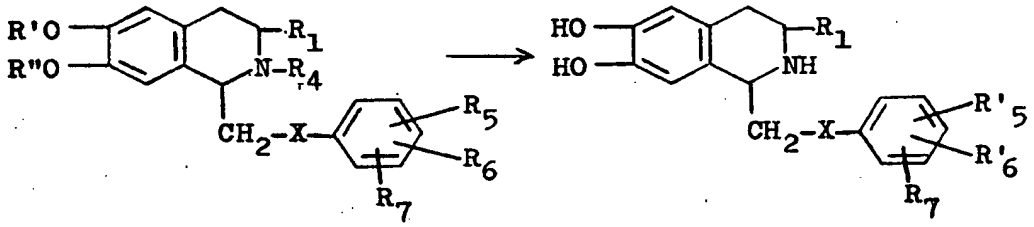
Example 9

In methanol (40 ml) was dissolved 1-(4-benzyloxyphenyl)oxymethyl-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (500 mg) and thereto were added 10 % palladium-carbon (200 mg) and concentrated hydrochloric acid (2 ml). The mixture was subjected to a catalytic reduction at room

temperature and at atmosphere. After stopping the absorption of hydrogen, the reaction mixture was filtered. The filtrate was evaporated to dryness under a reduced pressure. The resulting residue was recrystallized from methanol-ether to give 1-(4-hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (160 mg), M.P. 262°C.

Examples 10 to 37

In the same manner as described in Examples 7 to 9, various compounds were prepared. The compounds are shown in Table I.



[IV] [I']

Table 1

Ex. No.	R_1	R'	R"	R_4	R_5	R_6	R_7	R'_5	R'_6	X	Property of the product
10	H	H	H	CH_3CO-	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	4-OCH_3	S	Amorphous
11	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	6-OCH_3	H	2-OCH_3	6-OCH_3	H	O	M.P. 199°-201.5°C
12	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	3-Cl	H	H	3-Cl	H	O	M.P. 244°-245°C
13	H	CH_3CO-	CH_3CO-	CH_3CO-	2-Cl	4-OCH_3	H	2-Cl	4-OCH_3	O	M.P. 215°-219°C
14	H	CH_3CO-	CH_3CO-	CH_3CO-	3-Cl	4-Cl	H	3-Cl	4-Cl	O	M.P. 99°C
15	H	CH_3CO-	CH_3CO-	CH_3CO-	4-F	H	H	4-F	H	O	M.P. 93°-95°C
16	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	3-CF_3	H	H	3-CF_3	H	O	M.P. 233°-235°C
17	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	2-Cl	H	H	2-Cl	H	S	M.P. 249°-251°C
18	H	CH_3CO-	CH_3CO-	CH_3CO-	4-OCH_3	H	H	4-OCH_3	H	S	M.P. 161°-162°C
19	H	CH_3CO-	CH_3CO-	CH_3CO-	4-F	H	H	4-F	H	S	M.P. 104°-107°C
20	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	2-F	H	H	2-F	H	S	M.P. 193°-195°C
21	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	S	Amorphous
22	H	CH_3CO-	CH_3CO-	CH_3CO-	2-$OCH_2C_6H_5$	H	H	2-OH	H	O	M.P. 239°-241°C
23	H	CH_3CO-	CH_3CO-	CH_3CO-	3-$OCH_2C_6H_5$	H	H	3-OH	H	O	M.P. 252°-254°C
24	H	CH_3CO-	CH_3CO-	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	O	M.P. 262°C

- to be continued -

Table 1 Continued

Ex. No.	R_1	R'	R"	R_4	R_5	R_6	R_7	R'_5	R'_6	X	Property of the product
25	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-OCH_3	H	H	4-OCH_3	H	O	M.P. 240°-243°C
26	CH_3	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	O	M.P. 156°C
27	H	CH_3CO-	CH_3CO-	CH_3CO-	4-NO_2	H	H	4-NO_2	H	O	M.P. 238°-240°C
28	H	CH_3CO-	CH_3CO-	CH_3CO-	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	4-OCH_3	O	M.P. 231°-232°C M.P. 255°-257°C
29	H	CH_3CO-	CH_3CO-	CH_3CO-	4-Cl	H	H	4-Cl	H	S	M.P. 200°-203°C
30	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-NH_2	H	H	4-NH_2	H	O	M.P. 287°-288°C
31	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-$NHCOCH_3$	H	H	4-NH_2	H	O	M.P. 287°-288°C
32	H	H	H	CH_3CO-	4-OH	H	H	4-OH	H	O	M.P. 262°C
33	H	-CH_2-		CH_3CO-	4-Cl	H	H	4-Cl	H	S	M.P. 200°-203°C
34	H	H	H	CH_3CO-	4-C_6H_5	H	H	4-C_6H_5	H	O	M.P. 242°-245°C
35	H	CH_3CO-	CH_3CO-	CH_3CO-	4-OC_6H_5	H	H	4-OC_6H_5	H	O	M.P. 222°-223.5°C
36	H	CH_3CO-	CH_3CO-	CH_3CO-	4-$N(CH_3)_2$	H	H	4-$N(CH_3)_2$	H	S	NMR: 6.72$^\tau$ (6H, S, -$N(CH_3)_2$), 3.44, 3.45 (each 1H, S, arom-H(5,8)) and 2.40 (4H, S, arom-H)
37	H	CH_3CO-	CH_3CO-	CH_3CO-	3-OCH_3	4-OCH_3	H	3-OCH_3	4-OCH_3	O	M.P. 229°-231°C

[Note] The property of the product in Table 1 was shown of the product in a form of hydrobromide in Example 25 and in a form of hydrochloride in other Examples.

Example 38

(a) In absolute ethanol (30 ml) was dissolved metal sodium (0.07 g) and thereto was added 4-chlorothiophenol (0.3 g) and further added in portions 1-chloromethyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.7 g) under ice-cooling. The mixture was stirred at room temperature for one hour and further at 50°C for one hour. Ethanol was distilled off under a reduced pressure. To the residue was added diluted hydrochloric acid to neutralize and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and distilled to remove the solvent. The resulting residue was treated with alcoholic hydrochloric acid. The precipitated crystallines were separated by filtration and recrystallized from ether-ethanol to give 1-(4-chlorophenyl)thiomethyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.3 g), M.P. 180° - 184°C.

(b) A mixture of 1-(4-chlorophenyl)thiomethyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (3.0 g), 99 % ethanol (30 ml) and concentrated hydrochloric acid (30 ml) was refluxed for 4.5 hours. The reaction mixture was concentrated under a reduced pressure and the resulting residue was recrystallized from ethanol-acetone to give 1-(4-chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.1 g), M.P. 200° - 203°C.

Example 39

In absolute ethanol (30 ml) was dissolved metal sodium (0.13 g), and thereto were added 4-chlorothiophenol

(0.45 g) and further 1-chloromethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.7 g) under ice-cooling. The mixture was stirred for one hour under ice-cooling and further at room temperature for one hour. Ethanol was distilled off under a reduced pressure. The residue was made alkaline with ammonia and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and distilled to remove the solvent. The resulting residue was treated with alcoholic hydrochloric acid and the precipitated crystallines were separated by filtration and recrystallized from ethanol-ether to give 1-(4-chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (100 mg), M.P. 200° - 203°C.

Example 40

A mixture of 1-chloromethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.5 g), 4-fluorothiophenol (280 mg), 50 % sodium hydride (200 mg) and dry dimethylformamide (7 ml) was stirred at room temperature for one hour and further at 50°C for 1.5 hours. The reaction mixture was poured onto water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and distilled to remove the solvent. The residue was purified by silica gel chromatography. The product was converted into its hydrochloride by a conventional method to give 1-(4-fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (50 mg), M.P. 104° - 107°C.

Example 41

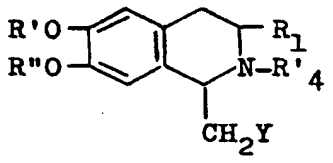
(a) A mixture of 1-chloromethyl-2-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (0.1 g), sodium 3,4,5-trimethoxyphenolate (81 mg) and dry dimethylformamide

(3 ml) was stirred at room temperature for 30 minutes and further at 50°C for 2 hours. The reaction mixture was poured onto water (60 ml) and thereto was added diluted hydrochloric acid to make acidic and then the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and distilled to remove the solvent. The resulting residue was crystallized from ethyl acetate-n-hexane to give 1-(3,4,5-trimethoxyphenyl)oxymethyl-2-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, M.P. 124°C (dec).

(b) A mixture of 1-(3,4,5-trimethoxyphenyl)oxymethyl-2-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (620 mg), concentrated hydrochloric acid (20 ml) and methanol (100 ml) was refluxed for 16 hours. The reaction mixture was evaporated to dryness under a reduced pressure. The residue was washed with ethyl acetate and chloroform and then dissolved in isopropanol, and therto was added ether. The mixture was allowed to stand. The precipitated crystallines were separated by filtration and dried to give 1-(3,4,5-trimethoxyphenyl)-oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (320 mg), M.P. 231° - 232°C and 255° - 257°C.

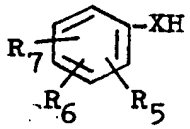
Examples 42 to 66

In the same manner as described in Examples 38 to 41, various compounds were prepared. The compounds are shown in Table 2.

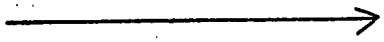


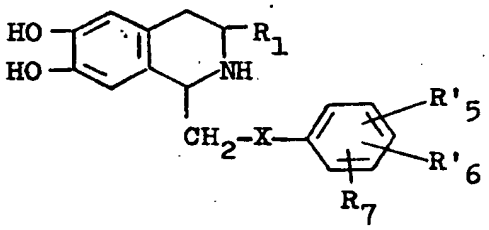
[V']

+



[VI]





[I']

Table 2

Ex. No.	R_1	R'	R"	R'4	R_5	R_6	R_7	R'5	R'6	X	Property of the product
42	H	H	H	CH_3CO-	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	4-OCH_3	S	Amorphous
43	H	H	H	CH_3CO-	6-OCH_3	H	2-OCH_3	6-OCH_3	H	O	M.P. 199°-201.5°C
44	H	H	H	CH_3CO-	3-Cl	H	H	3-Cl	H	O	M.P. 244°-245°C
45	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	2-Cl	4-OCH_3	H	2-Cl	4-OCH_3	O	M.P. 215°-219°C
46	H	H	H	CH_3CO-	3-Cl	4-Cl	H	3-Cl	4-Cl	O	M.P. 99°C
47	H	H	H	CH_3CO-	4-F	H	H	4-F	H	O	M.P. 93°-95°C
48	H	H	H	CH_3CO-	3-CF_3	H	H	3-CF_3	H	O	M.P. 233°-235°C
49	H	H	H	H	2-Cl	H	H	2-Cl	H	S	M.P. 249°-251°C
50	H	CH_3CO-	CH_3CO-	CH_3CO-	4-OCH_3	H	H	4-OCH_3	H	S	M.P. 161°-162°C
51	H	CH_3CO-	CH_3CO-	CH_3CO-	4-F	H	H	4-F	H	S	M.P. 104°-107°C
52	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	2-F	H	H	2-F	H	S	M.P. 193°-195°C
53	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	S	Amorphous
54	H	H	H	CH_3CO-	2-$OCH_2C_6H_5$	H	H	2-OH	H	O	M.P. 239°-241°C
55	H	H	H	CH_3CO-	3-$OCH_2C_6H_5$	H	H	3-OH	H	O	M.P. 252°-254°C
56	H	H	H	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	O	M.P. 262°C

- to be continued -

Table 2 Continued

Ex. No.	R_1	R'	R''	R'_4	R_5	R_6	R_7	R'_5	R'_6	X	Property of the product
57	H	H	H	CH_3CO-	4-OCH_3	H	H	4-OCH_3	H	O	M.P. 240°-243°C
58	CH_3	H	H	CH_3CO-	4-$OCH_2C_6H_5$	H	H	4-OH	H	O	M.P. 156°C
59	H	H	H	CH_3CO-	4-NO_2	H	H	4-NO_2	H	O	M.P. 238°-240°C
60	H	H	H	$C_6H_5CH_2-$	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	4-OCH_3	O	M.P. 231°-232°C M.P. 255°-257°C
61	H	CH_3CO-	CH_3CO-	CH_3CO-	4-Cl	H	H	4-Cl	H	S	M.P. 200°-203°C
62	H	H	H	CH_3CO-	4-NH_2	H	H	4-NH_2	H	O	M.P. 287°-288°C
63	H	H	H	CH_3CO-	4-C_6H_5	H	H	4-C_6H_5	H	O	M.P. 242°-245°C
64	H	CH_3CO-	CH_3CO-	CH_3CO-	4-OC_6H_5	H	H	4-OC_6H_5	H	O	M.P. 222°-223.5°C
65	H	CH_3CO-	CH_3CO-	CH_3CO-	4-$N(CH_3)_2$	H	H	4-$N(CH_3)_2$	H	S	NMR: 6.72$^\tau$ (6H, S, $-N(CH_3)_2$), 3.44, 3.45 (each 1H, S, arom-H(5,8)) and 2.40 (4H, S, arom-H)
66	H	CH_3CO-	CH_3CO-	CH_3CO-	3-OCH_3	4-OCH_3	H	3-OCH_3	4-OCH_3	O	M.P. 229°-231°C
66'	H	CH_3CO-	CH_3CO-	CH_3CO-	4-Cl	H	H	4-Cl	H	O	M.P. 226°C

[Note] The property of the product in Table 2 was shown of the product in a form of hydrobromide in Example 57 and in a form of hydrochloride in other Examples.

Example 67

In methanol (20 ml) was dissolved 1-(4-chlorophenyl)-thiomethyl-2-benzyl-6,7-dibenzyloxy-3,4-dihydroisoquinolinium bromide (200 mg) and thereto were added 10 % palladium-carbon (100 mg) and concentrated hydrochloric acid (0.5 ml). The mixture was subjected to a catalytic reduction under passing through hydrogen gas at room temperature and at atmosphere. After stopping the absorption of hydrogen, the reaction mixture was filtered. The filtrate was concentrated to dryness under a reduced pressure. The resulting residue was crystallized from ethanol-ether and the crystallines thus obtained were recrystallized from ethanol-ether to give 1-(4-chlorophenyl)-thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 200° - 203°C.

Example 68

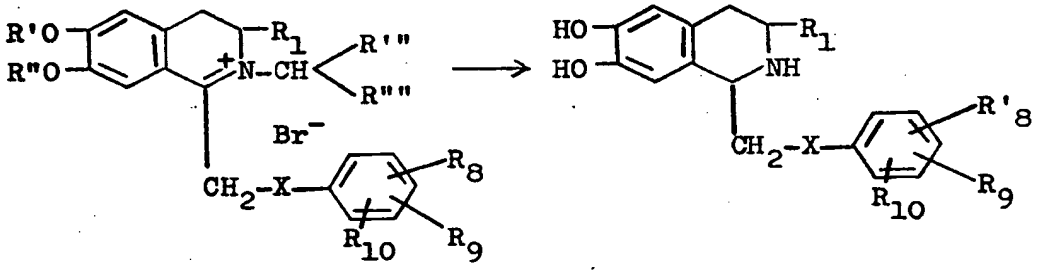
(a) In methanol (10 ml) was dissolved 1-(4-chlorophenyl)thiomethyl-2-benzyl-6,7-dibenzyloxy-3,4-dihydroisoquinolinium bromide (100 mg) and thereto was added an excess amount of sodium borohydride under ice-cooling. The mixture was stirred at room temperature for 4 hours. Methanol was distilled off from the reaction mixture under a reduced pressure. To the residue was added water and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and distilled to remove the solvent. The resulting residue was purified by alumina column chromatography (developer: benzene) to give 1-(4-chlorophenyl)thiomethyl-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline, M.P.

72° - 74°C.

(b) In methanol (40 ml) was dissolved 1-(4-chlorophenyl)thiomethyl-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (500 mg) and thereto were added 10 % palladium-carbon (200 mg) and concentrated hydrochloric acid (2 ml). The mixture was subjected to a catalytic reduction under passing through hydrogen gas at room temperature and at atmosphere. After stopping the absorption of hydrogen, the reaction mixture was filtered. The filtrate was concentrated to dryness under a reduced pressure. The residue was crystallized from methanol-ether to give 1-(4-chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (160 mg), M.P. 200° - 203°C.

Examples 69 to 92

In the same manner as described in Examples 67 and 68, various compounds were prepared. The compounds are shown in Table 3.



[VII] [I"]

Table 3

Ex. No.	R_1	R'	R"	R'"	R""	R_8	R_9	R_{10}	R'_8	X	Property of the product
69	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	S	Amorphous
70	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	2-OCH_3	6-OCH_3	H	2-OCH_3	O	M.P. 199°-201.5°C
71	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	3-Cl	H	H	3-Cl	O	M.P. 244°-245°C
72	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	2-Cl	4-OCH_3	H	2-Cl	O	M.P. 215°-219°C
73	H	CH_3CO-	CH_3CO-	CH_3-	OCH_3	3-Cl	4-Cl	H	3-Cl	O	M.P. 99°C
74	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	OCH_3	4-F	H	H	4-F	O	M.P. 93°-95°C
75	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	3-CF_3	H	H	3-CF_3	O	M.P. 233°-235°C
76	H	H	H	H	C_6H_5	2-Cl	H	H	2-Cl	S	M.P. 249°-251°C
77	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-OCH_3	H	H	4-OCH_3	S	M.P. 161°-162°C
78	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-F	H	H	4-F	S	M.P. 104°-107°C
79	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	2-F	H	H	2-F	S	M.P. 193°-195°C
80	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-Cl	H	H	4-Cl	O	M.P. 227°C
81	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-OH	H	H	4-OH	S	Amorphous
82	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	2-OH	H	H	2-OH	O	M.P. 239°-241°C
83	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	3-OH	H	H	3-OH	O	M.P. 252°-254°C

- to be continued -

Table 2 Continued

Ex. No.	R_1	R'	R"	R"'	R""	R_8	R_9	R_{10}	R'8	X	Property of the product
84	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-OH	H	H	4-OH	O	M.P. 262°C
85	H	H	H	H	C_6H_5	4-OCH_3	H	H	4-OCH_3	O	M.P. 240°-243°C
86	CH_3	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-OH	H	H	4-OH	O	M.P. 156°C
87	H	H	H	H	C_6H_5	4-NO_2	H	H	4-NH_2	O	M.P. 287°-288°C
88	H	H	H	H	C_6H_5	3-OCH_3	4-OCH_3	5-OCH_3	3-OCH_3	O	M.P. 231°-232°C M.P. 255°-257°C
89	H	H	H	H	C_6H_5	4-C_6H_5	H	H	4-C_6H_5	O	M.P. 242°-245°C
90	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-OC_6H_5	H	H	4-OC_6H_5	O	M.P. 222°-223.5°C
91	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	4-$N(CH_3)_2$	H	H	4-$N(CH_3)_2$	S	NMR: 6.72τ (6H, S, -$N(CH_3)_2$), 3.44, 3.45 (each 1H, S, arom-H(5,8) and 2.40 (4H, S, arom-H)
92	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	C_6H_5	3-OCH_3	4-OCH_3	H	3-OCH_3	O	M.P. 229°-231°C

[Note] The property of the product in Table 3 was shown of the product in a form of hydrobromide in Example 85 and in a form of hydrochloride in other Examples.

Example 93

A mixture of 2-(4-chlorophenoxy)malonaldehyde-acid ethyl ester (2.7 g), 3,4-dihydroxyphenethylamine hydrochloride (1.5 g), 10 % hydrochloric acid (27 ml) and methanol (27 ml) was refluxed on oil bath for 16 hours. The reaction mixture was evaporated to dryness under a reduced pressure. To the resulting residue was added ethyl acetate and the precipitates were prepared by filtration and recrystallized from water to give colorless, granular crystals (1.0 g) of 1-(4-chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 227°C (dec).

Example 94

A mixture of 2-(4-methoxyphenoxy)malonaldehyde-acid ethyl ester (3.6 g), 3,4-dihydroxyphenethylamine hydrochloride (2.0 g), 10 % hydrochloric acid (36 ml) and methanol (36 ml) was refluxed for 14 hours. After the reaction, methanol was distilled off under a reduced pressure. The aqueous layer thus obtained was washed with ethyl acetate and concentrated to dryness under a reduced pressure. To the residue was added 99 % ethanol and the precipitated crystallines were separated by filtration and recrystallized from 95 % ethanol-ether to give colorless crystals (1.1 g) of 1-(4-methoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 250° - 252°C (dec).

Example 95

A mixture of 2-(4-chlorophenylthio)malonaldehyde-acid

ethyl ester (2.6 g), 3,4-dihydroxyphenethylamine hydrochloride (1.4 g), 10 % hydrochloric acid (27 ml) and methanol (27 ml) was refluxed for 16 hours. After the reaction, the mixture was evaporated to dryness under a reduced pressure and to the residue was added ethyl acetate. The resulting precipitates were separated by filtration and recrystallized from 99 % ethanol to give colorless powder (1.2 g) of 1-(4-chlorophenyl)-thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 200° - 203°C (dec).

Examples 96 to 121

In the same manner as described in Examples 93 to 95, the following compounds were prepared.

(96) 1-(3,4-Dichlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 99°C

(97) 1-(3,4,5-Trimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 231° - 232°C and 255° - 257°C

(98) 1-(3-Trifluoromethylphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 233° - 235°C

(99) 1-(4-Nitrophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 238° - 240°C

(100) 1-(4-Aminophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 287° - 288°C

(101) 1-(4-Hydroxyphenyl)oxymethyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 156°C

(102) 1-(3-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 252° - 254°C

(103) 1-(2-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 239° - 241°C

(104) 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, amorphous

(105) 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 193° - 195°C

(106) 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 104° - 107°C

(107) 1-(4-Hydroxyphenyl)oxymethyl-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 231° - 232°C

(108) 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 161° - 162°C

(109) 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 249° - 251°C

(110) 1-(4-Fluorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 93° - 95°C

(111) 1-(2-Chloro-4-methoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 215° - 219°C

(112) 1-(3-Chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 244° - 245°C

(113) 1-(4-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 262°C

(114) 1-(2,6-Dimethoxyphenyl)oxymethyl-6,7-dihydroxy-

1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 199° - 201.5°C

(115) 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, amorphous

(116) 1-(3,4-Methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 227°C (dec).

(117) 1-(4-Benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 195° - 197°C

(118) 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 242° - 245°C (dec)

(119) 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 222° - 223.5°C

(120) 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride, NMR spectrum: 6.72τ (6H, S, $-N(CH_3)_2$), 3.44, 3.45 [each 1H, S, arom-H (5,8)] and 2.40 (4H, S, arom-H)

(121) 1-(3,4-Dimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 229° - 231°C

(121') 1-(4-Methanesulfonamidophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 253° - 255°C

Example 122

A mixture of 3,4-dihydroxyphenethylamine hydrochloride (0.12 g), 2-(4-chlorophenoxy)vinyl acetate (0.2 g), methanol (5 ml), water (1 ml) and 10% hydrochloric acid (1 drop) was refluxed for 22 hours. After the reaction, methanol was distilled off under a reduced pressure and the residue was dissolved in water. The aqueous layer was washed with

B

chloroform (three times) and ether (once). After treating with charcoal, the aqueous layer was distilled under a reduced pressure to remove water. To the resulting residue was added ethanol (1 ml). The precipitated crystallines were separated by filtration and dried to give colorless crystals (100 mg) of 1-(4-chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 225° - 226.5°C

Example 123

A mixture of 3,4-dihydroxyphenethylamine hydrochloride (0.1 g), 2-(4-chlorophenylthio)ethane-1,1-diol diacetate (0.4 g), n-butanol (10 ml), water (2 ml) and 10 % hydrochloric acid (1 drop) was refluxed for 15 hours. After the reaction, n-butanol was distilled off and the residue was dissolved in water. The aqueous layer was washed with chloroform (twice) and ether (once) and distilled under a reduced pressure to remove water. To the resulting residue was added acetone. The precipitated crystallines were separated by filtration to give colorless, granular crystals (80 mg) of 1-(4-chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 200° - 203°C.

Example 124

A mixture of 3,4-dihydroxyphenethylamine hydrochloride (0.2 g), 2-(4-chlorophenylthio)acetaldoxime (0.43 g), n-butanol (10 ml), water (2 ml) and 10 % hydrochloric acid (10 drops) was refluxed for 20 hours. After the reaction, n-butanol was distilled off under a reduced pressure. The residue was dissolved in water and then made alkaline with aqueous ammonia. The mixture was extracted with chloroform (three times). The extract was washed with water and then extracted with diluted hydrochloric acid. The diluted hydro-

chloric acid layer was washed with ether, and then treated with charcoal and distilled under a reduced pressure. The resulting residue was dissolved in acetone (2 ml) and thereto was added a small amount of ether. The resulting crystallines were separated by filtration to give colorless crystals (0.1 g) of 1-(4-chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 200° - 203°C.

Example 125

A mixture of 3,4-dihydroxyphenethylamine hydrochloride (0.1 g), 2-(4-chlorophenoxy)acetaldoxime (0.196 g), n-butanol (10 ml), water (1 ml) and 10 % hydrochloric acid (5 drops) was refluxed for 20 hours. After the reaction, n-butanol was distilled off under a reduced pressure. The residue was dissolved in water and made alkaline with aqueous potassium carbonate solution. The mixture was extracted with chloroform (three times). The extract was washed with water and then extracted with diluted hydrochloric acid. The diluted hydrochloric acid layer was washed with ether, treated with charcoal and then distilled under a reduced pressure. The resulting residue was dissolved in acetone (1.5 ml) and thereto was added a small amount of ether. The precipitated crystallines were separated by filtration to give colorless powdery crystals (45 mg) of 1-(4-chlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 225° - 226°C

Example 126

A mixture of 3,4-dihydroxyphenethylamine hydrochloride (0.2 g), 2-(4-methoxyphenoxy)acetaldoxime (0.39 g), n-butanol (10 ml), water (2 ml) and 10 % hydrochloric acid (10 drops) was refluxed for 20 hours. After the reaction,

n-butanol was distilled off under a reduced pressure. The residue was dissolved in water and then made alkaline with aqueous ammonia. The mixture was extracted with chloroform (three times). The chloroform layer was washed with water and extracted with diluted hydrochloric acid. The diluted hydrochloric acid layer was treated with charcoal and then distilled under a reduced pressure to remove water. To the residue was added acetone. The precipitated crystallines were separated by filtration to give 1-(4-methoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (160 mg), M.P. 251° - 252°C (dec).

Examples 127 to 152

In the same manner as described in Examples 122 to 126, the following compounds were prepared.

(127) 1-(3,4-Dichlorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 99°C

(128) 1-(3,4,5-Trimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 231° - 232°C and 255° - 257°C

(129) 1-(3-Trifluoromethylphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 233° - 235°C

(130) 1-(4-Nitrophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 238° - 240°C

(131) 1-(4-Aminophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 287° - 288°C

(132) 1-(4-Hydroxyphenyl)oxymethyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P.

156°C

(133) 1-(3-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 252° - 254°C

(134) 1-(2-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 239° - 241°C

(135) 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, amorphous

(136) 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 193° - 195°C

(137) 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 104° - 107°C

(138) 1-(4-Hydroxyphenyl)oxymethyl-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 231° - 232°C

(139) 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 161° - 162°C

(140) 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 249° - 251°C

(141) 1-(4-Fluorophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 93° - 95°C

(142) 1-(2-Chloro-4-methoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 215° - 219°C

(143) 1-(3-Chlorophenyl)oxymethyl-6,7-dihydroxy-

1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 244° - 245°C

(144) 1-(4-Hydroxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 262°C

(145) 1-(2,6-Dimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 199° - 201.5°C

(146) 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, amorphous

(147) 1-(3,4-Methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 227°C (dec)

(148) 1-(4-Benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 195° - 197°C

(149) 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 242° - 245°C

(150) 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 222° - 223.5°C

(151) 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride, NMR spectrum: 6.72 τ (6H, S, $-N(CH_3)_2$), 3.44, 3.45 [each 1H, S, arom-H(5,8)] and 2.40 (4H, S, arom-H)

(152) 1-(3,4-Dimethoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 229° - 231°C

(153) 1-(4-Methansulfonamidephenyl)oxymethyl-6,7-dihydroxy 1,2,3,4-tetrahydroisoquinoline hydrochloride, M.P. 253° - 255°C

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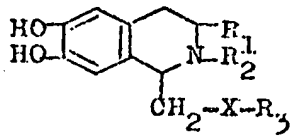
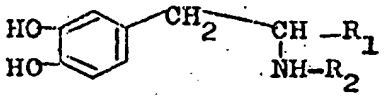
The embodiments of the invention in which an exclusive property or process is claimed are defined as follows:-

1. A process for preparing 1,2,3,4-tetrahydroisoquinoline of the general formula:



wherein R_1 and R_2 are each hydrogen or lower alkyl group, R_3 is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, mono- or di(lower)alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy, phenoxy which may be substituted by lower alkyl, phenyl(lower)alkoxy which may be substituted with lower alkyl and phenyl which may be substituted with lower alkyl, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises,

(a) reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



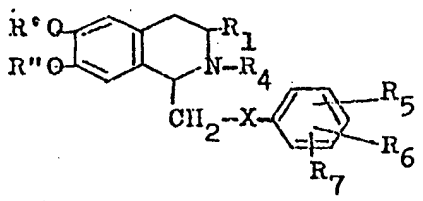
wherein R_1 and R_2 are each as defined above, or its salt with an acetaldehyde derivative of the formula:

$$R_3'\text{-X-CH}_2\text{CHO}$$

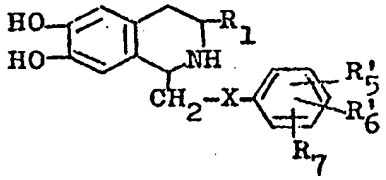
wherein X is as defined above, and R_3' is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of lower alkylenedioxy, phenyl(lower)alkoxy which may be substituted with lower alkyl, phenoxy which may be substituted with lower alkyl, phenyl which may be substituted with lower alkyl, mono- or di(lower)alkyl amino, and alkanesulfonamido, or its acetal, hemiacetal or hydrate to give a compound of the formula:

wherein R_1, R_2, R_3' and X are each as defined above, or its salt thereof; or

(b) subjecting a 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline of the formula:

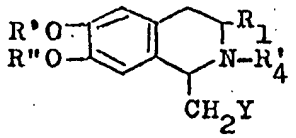


wherein R_1 is hydrogen or lower alkyl group, R' and R" are hydrogen or a protecting group of hydroxy group, R_4 is a protecting group of imino group, R_5 is hydroxy, hydroxy which is protected with protecting group for hydroxy, amino, amino which is protected with protecting group for amino, mono- or di(lower)alkyl amino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl or phenyl which may be substituted with lower alkyl, R_6 is hydrogen, hydroxy, hydroxy which is protected with protecting group for hydroxy, amino, amino which is protected with protecting group for amino, lower alkoxy or halogen, R_7 is hydrogen or lower alkoxy, and X is as defined above, to a reaction for removing the protecting group(s) to give a compound of the formula:

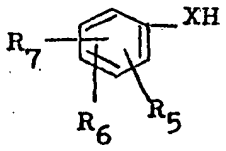


wherein R_1, R_7 and X are each as defined above, R_5' is hydroxy, amino, mono- or di(lower)alkyl amino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl or phenyl which may be substituted with lower alkyl group, and R_6' is hydrogen, hydroxy, amino, lower alkoxy or halogen, or the salt thereof; or

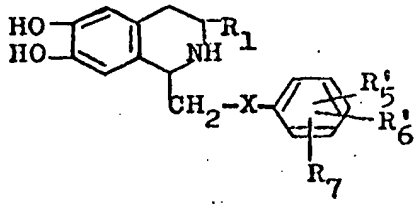
(c) reacting a compound of the formula:



wherein R_1, R' and R" are each as defined above, R_4' is hydrogen or a protecting group of imino, and Y is a residue of an acid, or its salt with a benzene derivative of the formula:

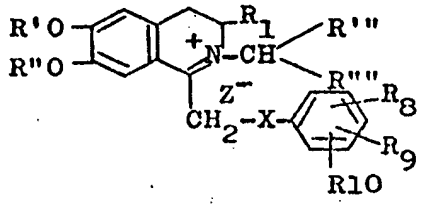


wherein R_5, R_6, R_7 and X are each as defined above, and if necessary, subjecting the resulting compound to a reaction for removing the protecting group(s) to give a compound of the formula:

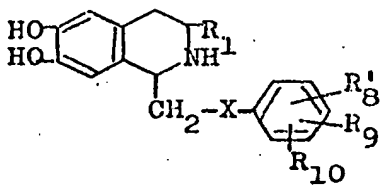


wherein R_1, R_5', R_6', R_7 and X are each as defined above, or the salt thereof; or

(d) reducing an immonium compound of the formula:

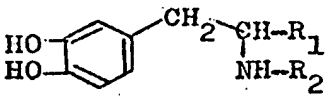


wherein R_1, R', R" and X are each as defined above, R'" is hydrogen or lower alkyl, R"" is phenyl or lower alkoxy, R_8 is hydroxy, lower alkoxy, nitro, amino, mono- or di(lower)alkyl amino, phenoxy, halogen, halo(lower)alkyl or phenyl which may be substituted with lower alkyl, R_9 is hydrogen, hydroxy, lower alkoxy or halogen, R_{10} is hydrogen or lower alkoxy, and Z is a residue of an acid, to give a compound of the formula:



wherein R_1, R_9, R_{10} and X are each as defined above, and R'_8 is hydroxy, lower alkoxy, amino, mono- or di(lower)alkyl amino, phenyl which may be substituted with lower alkyl, phenoxy, halogen or halo(lower)alkyl, or the salt thereof;or

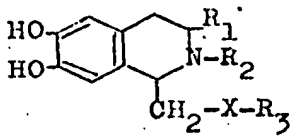
(e) reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



wherein R_1 and R_2 are each as defined above, or its salt with a malonaldehyde-acid derivative of the formula:

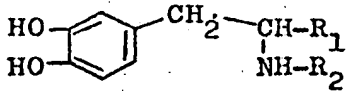
$$R_3\text{-}X\text{-}Y'\text{-}Z'$$

wherein R_3 and X are each as defined above, Y' is formylmethylene or a group convertible thereto under an acidic condition, and Z' is carboxy group or its derivative, to give a compound of the formula:



wherein R_1, R_2, R_3 and X are each as defined above, or the salt thereof; or

(f) reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



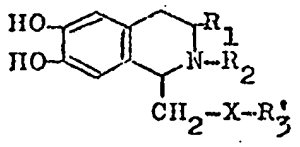
wherein R_1 and R_2 are each as defined above, or its salt with a compound of the formula:

$$R_3\text{-}X\text{-}Y''$$

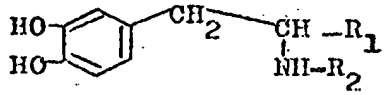
wherein R_3 and X are each as defined above, and Y" is formylmethyl wherein the formyl group is in a form of mono or diacyldiol, thioacetal , hemithioacetal, Schiff's base, oxime, semicarbazone or thiosemicarbazone; (2-acyloxy)vinyl; (2-lower alkoxy)vinyl; (2-lower alkylthio)vinyl; or (2-amino)vinyl, to give a compound of the formula:

wherein R_1, R_2, R_3 and X are each as defined above, or the salt thereof; and if necessary, converting the compound obtained by anyone of the steps from (a) to (f) into its acid salt by treating it with a pharmaceutically acceptable acid.

2. A process for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 and R_2 are each hydrogen or lower alkyl, R_3' is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of lower alkylenedioxy, benzyloxy which may be substituted with methyl, phenoxy which may be substituted with methyl, phenyl which may be substituted with methyl, di(lower) alkyl amino, and alkanesulfonamido, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:

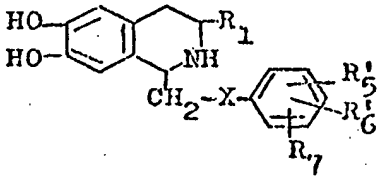


wherein R_1 and R_2 are each as defined above, or its salt with an acetaldehyde derivative of the formula:

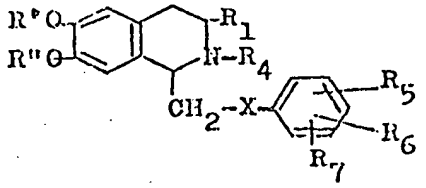
$$R_3'\text{-X-CH}_2\text{CHO}$$

wherein R_3' and X are each as defined above, or its acetal, hemiacetal or hydrate, and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

3. A process according to claim 1(b) for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:

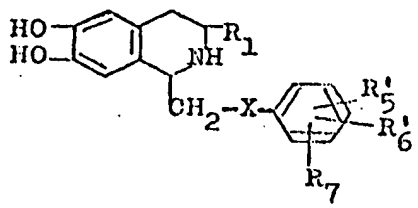


wherein R_1 is hydrogen or lower alkyl, R_5' is hydroxy, amino, di(lower) alkyl amino. lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl or phenyl which may be substituted with methyl, R_6' is hydrogen, lower alkoxy or halogen, R_7 is hydrogen or lower alkoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises subjecting a 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivative of the formula:

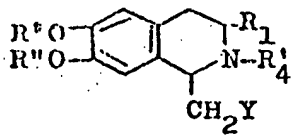


wherein R_1, R_7 and X are each as defined above, R' and R" are hydrogen or a protecting group of hydroxy group, R_4 is a protecting group of imino group, R_5 is hydroxy, hydroxy which is protected with protecting group for hydroxy, amino, amino which is protected with protecting group for amino, di(lower)alkyl amino, lower alkoxy, phenoxy, nitro, halogen, or halo(lower)alkyl or phenyl which may be substituted with methyl, and R_6 is hydrogen, lower alkoxy or halogen, to a reaction for removing the protecting group(s) , and if necessary , converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

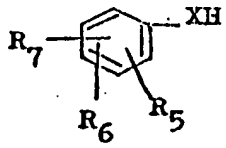
4. A process according to claim 1(c) for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 is hydrogen or lower alkyl, R_5' is hydroxy, amino, di(lower)alkyl amino, lower alkoxy, phenoxy, nitro, halogen, halo(lower)alkyl or phenyl which may be substituted with methyl, R_6' is hydrogen, lower alkoxy or halogen, R_7 is hydrogen or lower alkoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula:

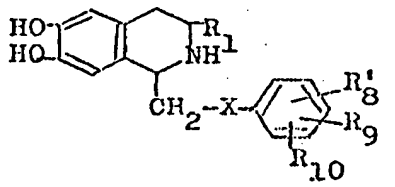


wherein R_1 is as defined above, R' and R" are hydrogen or a protecting group for hydroxy group, R_4' is hydrogen or a protecting group for imino group, and Y is a residue of an acid, or its salt with a benzene derivative of the formula:

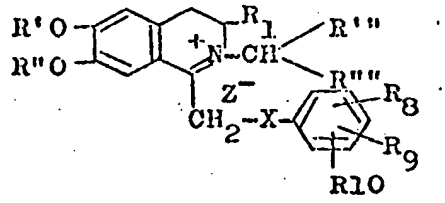


wherein R_7 and X are each as defined above, R_5 is hydroxy, hydroxy which is protected with protecting group for hydroxy, amino, amino which is protected with protecting group for amino group, di(lower) alkyl amino, lower alkoxy, phenoxy, nitro, halogen, or halo(lower)-alkyl or phenyl which may be substituted with methyl, and R_6 is hydrogen, lower alkoxy or halogen, and if necessary, subjecting the resulting compound to a reaction for removing the protecting group(s), and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

5. A process according to claim 1(d) for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:

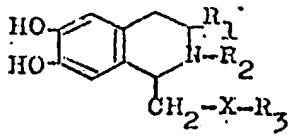


wherein R_1 is hydrogen or lower alkyl, R_8' is hydroxy, lower alkoxy, amino, di(lower)alkyl amino, phenoxy, halogen, halo(lower)alkyl or phenyl which may be substituted with methyl, R_9 is hydrogen, lower alkoxy or halogen, R_{10} is hydrogen or lower alkoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reducing an immonium compound of the formula:

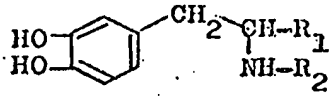


wherein R_1, R_9, R_{10} and X are each as defined above, R' and R" are hydrogen or a protecting group for hydroxy, R"' is hydrogen or lower alkyl, R"" is phenyl or lower alkoxy, R_8 is hydroxy, lower alkoxy, nitro, amino, di(lower)alkyl amino, phenoxy, halogen, halo-(lower)alkyl or phenyl which may be substituted with methyl, and Z is a residue of an acid, and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

6. A process according to claim 1(e) for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 and R_2 are each hydrogen or lower alkyl group, R_3 is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, di(lower)alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy, phenoxy which may be substituted with methyl, benzyloxy which may be substituted with methyl and phenyl which may be substituted with methyl, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:

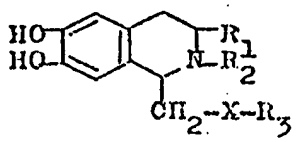


wherein R_1 and R_2 are each as defined above, or its salt with a malonaldehyde-acid derivative of the formula:

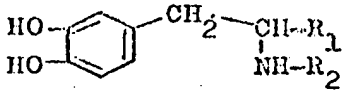
$$R_3\text{-}X\text{-}Y'\text{-}Z'$$

wherein R_3 and X are each as defined above, Y' is formylmethylene or a group convertible thereto under an acidic condition, and Z' is carboxy group or its derivative, and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

7. A process according to claim 1(f) for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 and R_2 are each hydrogen or lower alkyl group, R_3 is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of hydroxy, halogen, halo(lower)alkyl, nitro, amino, di(lower)-alkyl amino, alkanesulfonamido, lower alkoxy, lower alkylenedioxy, phenoxy which may be substituted with methyl, benzyloxy which may be substituted with methyl and phenyl which may be substituted with methyl, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:

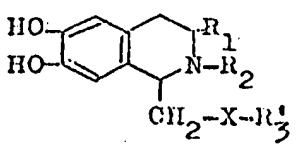


wherein R_1 and R_2 are each as defined above, or its salt with a compound of the formula:

$$R_3\text{-}X\text{-}Y''$$

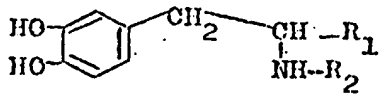
wherein R_3 and X are each as defined above, and Y" is formyl-methyl wherein the formyl group is in a form of mono or diacyl-diol, thioacetal , hemithioacetal, Schiff's base, oxime, semicarbazone or thiosemicarbazone; (2-acyloxy)vinyl; (2-lower alkoxy)vinyl; (2-lower alkylthio)vinyl; or (2-amino)vinyl, and if necessary, converting the resultant into its acid salts by treating it with a pharmaceutically acceptable acid.

8. A process according to claim 2 for preparing 1,2,3,4-tetra.-hydroisoquinolines of the formula:



B

wher... R_1 and R_2 are both hydrogen, R_3' is phenyl group which is substituted with a group selected from a group consisting of methylenedioxy, benzyloxy, phenoxy, phenyl, dimethylamino and methanesulfonamido, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



wherein R_1 and R_2 are each as defined above, or its salt with an acetaldehyde derivative of the formula:

$$R_3'\text{-}X\text{-}CH_2CHO$$

wherein R_3' and X are each as defined above, or its acetal, and if necessary, converting the resultant into its acid salts by treating it with a pharmaceutically acceptable acid.

9. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 3,4-methylenedioxyphenyl and X is oxygen.

10. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 4-benzyloxyphenyl and X is oxygen.

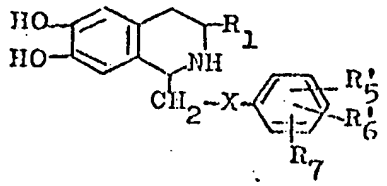
11. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 4-phenoxyphenyl and X is oxygen.

12. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 4-biphenylyl and X is oxygen.

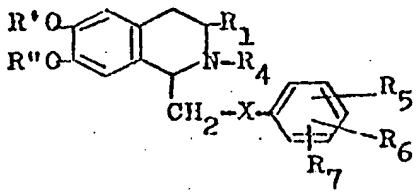
13. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 4-dimethylaminophenyl and X is sulfur.

14. A process according to claim 8, wherein R_1 and R_2 are both hydrogen, R_3' is 4-methanesulfonamidophenyl and X is oxygen.

15. A process according to claim 3 for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 is hydrogen or methyl, R_5' is hydroxy, amino, dimethylamino, methoxy, phenyl, phenoxy, nitro, chlorine, fluorine or trifluoromethyl, R_6' is hydrogen, methoxy or chlorine, R_7 is hydrogen or methoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises subjecting a 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline derivative of the formula:



wherein R_1, R_7 and X are each as defined above, R' and R" are hydrogen, acetyl, benzyl or bound together to form methylene, R_4 is acetyl or benzyl, R_5 is hydroxy, benzyloxy, amino, acetamido, dimethylamino, methoxy, phenyl, phenoxy, nitro, chlorine, fluorine or trifluoromethyl, and R_6 is hydrogen, methoxy or chlorine, to a reaction for removing the protecting group(s), and if necessary, converting the resultant into its acid salts by treating it with a pharmaceutically acceptable acid.

16. A process according to claim 15, wherein

R_1 is hydrogen,

R' and R" are both acetyl,

R_4 is acetyl,

R_5 and R_5' are both 4-chloro,

R_6 and R_6' are both hydrogen,

R_7 is hydrogen and
X is oxygen.

17. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4 is acetyl,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

18. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is benzyl,
R_5 is 4-benzyloxy , R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

19. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4 is acetyl,
R_5 and R_5' are both 3-methoxy,
R_6 and R_6' are both 4-methoxy,
R_7 is 5-methoxy and
X is sulfur.

20. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 6-methoxy,
R_6 and R_6' are both hydrogen,

R_7 is 2-methoxy and
X is oxygen.

21. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 3-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

22. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 2-chloro,
R_6 and R_6' are both 4-methoxy,
R_7 is hydrogen and
X is oxygen.

23. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 3-chloro,
R_6 and R_6' are both 4-chloro,
R_7 is hydrogen and
X is oxygen.

24. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,

R_5 and R_5' are both 4-fluoro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

25. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 3-trifluoromethyl,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

26. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 2-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

27. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-methoxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

28. A process according to claim 15, wherein

R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-fluoro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

29. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 2-fluoro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

30. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 is 4-benzyloxy, R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

31. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 is 2-benzyloxy, R_5' is 2-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

32. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 is 3- benzyloxy, R_5' is 3-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

33. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 is 4-benzyloxy, R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

34. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 4-methoxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

35. A process according to claim 15, wherein
R_1 is methyl,
R' and R" are both benzyl,
R_4 is acetyl,

R_5 is 4-benzyloxy, R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

36. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-nitro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

37. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 3-methoxy,
R_6 and R_6' are both 4-methoxy,
R_7 is 5-methoxy and
X is oxygen.

38. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

39. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 and R_5' are both 4-amino,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

40. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4 is acetyl,
R_5 is 4-acetamido, R_5' is 4-amino,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

41. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4 is acetyl,
R_5 and R_5' are both 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

42. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are bound together to form methylene,

R_4 is acetyl,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

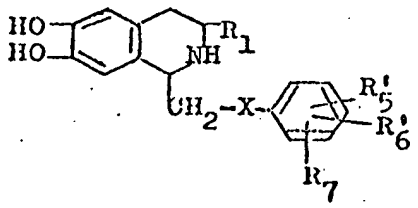
43. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4 is acetyl,
R_5 and R_5' are both 4-phenyl,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

44. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-phenoxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

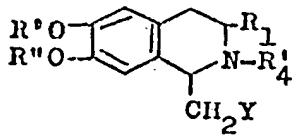
45. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 4-dimethylamino,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

46. A process according to claim 15, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R_5' are both 3-methoxy,
R_6 and R_6' are both 4-methoxy,
R_7 is hydrogen and
X is oxygen.

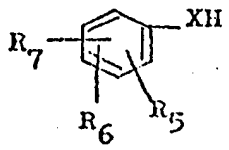
47. A process according to claim 4 for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 is hydrogen or methyl, R_5' is hydroxy, amino, dimethylamino, methoxy, phenyl, phenoxy, nitro, chlorine, fluorine or trifluoromethyl, R_6' is hydrogen, methoxy or chlorine, R_7 is hydrogen or methoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula:



wherein R_1 is as defined above, R' and R" are hydrogen, benzyl or acetyl, R_4' is hydrogen , benzyl or acetyl, and Y is chlorine, or its salt with a benzene derivative of the formula:



wherein R_7 and X are each as defined above, R_5 is hydroxy, benzyloxy, amino, dimethylamino, methoxy, phenyl, phenoxy, nitro, chlorine, fluorine or trifluoromethyl, and R_6 is hydrogen, methoxy or chlorine, and if necessary, subjecting the resulting compound to a reaction for removing the protecting group(s), and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

48. A process according to claim 47, wherein
R_1 is hydrogen ,
R' and R" are both benzyl,
R_4' is hydrogen,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

49. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is hydrogen,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

50. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both hydrogen,

R'_4 is hydrogen,

R_5 and R'_5 are both 4-fluoro,

R_6 and R'_6 are both hydrogen,

R_7 is hydrogen and

X is sulfur.

51. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both hydrogen,

R'_4 is acetyl,

R_5 and R'_5 are both 3-methoxy,

R_6 and R'_6 are both 4-methoxy,

R_7 is 5-methoxy and

X is oxygen.

52. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both hydrogen,

R'_4 is acetyl,

R_5 and R'_5 are both 3-methoxy,

R_6 and R'_6 are both 4-methoxy,

R_7 is 5-methoxy and

X is sulfur.

53. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both hydrogen,

R'_4 is acetyl,

R_5 and R'_5 are both 6-methoxy,

R_6 and R'_6 are both hydrogen,

R_7 is 2-methoxy and
X is oxygen.

54. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 and R_5' are both 3-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

55. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R_4' is acetyl,
R_5 and R_5' are both 2-chloro,
R_6 and R_6' are both 4-methoxy,
R_7 is hydrogen and
X is oxygen.

56. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 and R_5' are both 3-chloro,
R_6 and R_6' are both 4-chloro,
R_7 is hydrogen and
X is oxygen.

57. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,

R_5 and R_5' are both 4-fluoro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

58. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 and R_5' are both 3-trifluoromethyl,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

59. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 and R_5' are both 2-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

60. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4' is acetyl,
R_5 and R_5' are both 4-methoxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

61. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both acetyl,

R'_4 is acetyl,

R_5 and R'_5 are both 4-fluoro,

R_6 and R'_6 are both hydrogen,

R_7 is hydrogen and

X is sulfur.

62. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both benzyl,

R'_4 is acetyl,

R_5 and R'_5 are both 2-fluoro,

R_6 and R'_6 are both hydrogen,

R_7 is hydrogen and

X is sulfur.

63. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both benzyl,

R'_4 is acetyl,

R_5 is 4-benzyloxy, R'_5 is 4-hydroxy,

R_6 and R'_6 are both hydrogen,

R_7 is hydrogen and

X is sulfur.

64. A process according to claim 47, wherein

R_1 is hydrogen,

R' and R" are both hydrogen,

R'_4 is acetyl,

R_5 is 2-benzyloxy, R'_5 is 2-hydroxy,

R_6 and R'_6 are both hydrogen,

R_7 is hydrogen and

X is oxygen.

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65. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 is 3- benzyloxy, R_5' is 3-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

66. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 is 4-benzyloxy, R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

67. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4 is acetyl,
R_5 and R_5' are both 4-methoxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

68. A process according to claim 47, wherein
R_1 is methyl,
R' and R" are both hydrogen,
R_4' is acetyl,

R_5 is 4-benzyloxy, R_5' is 4-hydroxy,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

69. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is acetyl,
R_5 and R_5' are both 4-nitro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

70. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R_4' is benzyl,
R_5 and R_5' are both 3-methoxy,
R_6 and R_6' are both 4-methoxy,
R_7 is 5-methoxy and
X is oxygen.

71. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4' is acetyl,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is sulfur.

72. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R'_4 is acetyl,
R_5 and R'_5 are both 4-amino,
R_6 and R'_6 are both hydrogen,
R_7 is hydrogen and
X is oxygen.

73. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R'_4 is acetyl,
R_5 and R'_5 are both 4-phenyl,
R_6 and R'_6 are both hydrogen,
R_7 is hydrogen and
X is oxygen.

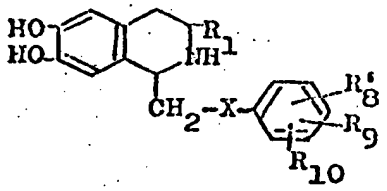
74. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R'_4 is acetyl,
R_5 and R'_5 are both 4-phenoxy,
R_6 and R'_6 are both hydrogen,
R_7 is hydrogen and
X is oxygen.

75. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4 is acetyl,
R_5 and R'_5 are both 4-dimethylamino,
R_6 and R'_6 are both hydrogen,
R_7 is hydrogen and
X is sulfur.

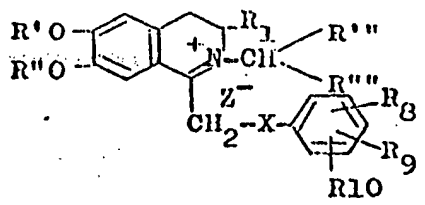
76. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4' is acetyl,
R_5 and R_5' are both 3-methoxy,
R_6 and R_6' are both 4-methoxy,
R_7 is hydrogen and
X is oxygen.

77. A process according to claim 47, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R_4' is acetyl,
R_5 and R_5' are both 4-chloro,
R_6 and R_6' are both hydrogen,
R_7 is hydrogen and
X is oxygen.

78. A process according to claim 5 for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 is hydrogen or methyl, R_8' is hydroxy, methoxy, amino, dimethylamino, phenyl, phenoxy, chlorine, fluorine or trifluoromethyl, R_9 is hydrogen, methoxy or chlorine, R_{10} is hydrogen or methoxy, and X is oxygen or sulfur, and the pharmaceutically acceptable salts thereof, which comprises reducing an immonium compound of the formula:



wherein R_1, R_9, R_{10} and X are each as defined above, R' and R" are hydrogen, benzyl or acetyl, R"' is hydrogen or methyl, R"" is phenyl or methoxy, R_8 is hydroxy, methoxy, nitro, dimethylamino, phenyl, phenoxy, chlorine, fluorine or trifluoromethyl, and Z is bromine, and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

79. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen,
R"" is phenyl,
R_8 and R_8' are both 4-chloro,
R_9 and R_{10} are both hydrogen and
X is sulfur.

80. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-methoxy,
R_9 is 4-methoxy, R_{10} is 5-methoxy and
X is sulfur.

81. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,

R_8 and R_8' are both 2-methoxy,
R_9 is 6-methoxy, R_{10} is hydrogen and
X is oxygen.

82. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-chloro,
R_9 and R_{10} are both hydrogen and
and X is oxygen.

83. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 2-chloro,
R_9 is 4-methoxy, R_{10} is hydrogen and
X is oxygen.

84. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both acetyl,
R"' is methyl, R"" is methoxy,
R_8 and R_8' are both 3-chloro,
R_9 is 4-chloro, R_{10} is hydrogen and
X is oxygen.

85. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is methoxy,
R_8 and R_8' are both 4-fluoro,
R_9 and R_{10} are both hydrogen and
X is oxygen.

86. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-trifluoromethyl,
R_9 and R_{10} are both hydrogen and
X is oxygen.

87. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R"' is hydrogen R"" is phenyl,
R_8 and R_8' are both 2-chloro,
R_9 and R_{10} are both hydrogen and
X is sulfur.

88. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-methoxy,
R_9 and R_{10} are both hydrogen and
X is sulfur.

89. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-fluoro,
R_9 and R_{10} are both hydrogen and
X is sulfur.

90. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 2-fluoro,
R_9 and R_{10} are both hydrogen and
X is sulfur.

91. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-chloro,
R_9 and R_{10} are both hydrogen and
X is oxygen.

92. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-hydroxy,
R_9 and R_{10} are both hydrogen and
X is sulfur.

93. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 2-hydroxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

94. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-hydroxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

95. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-hydroxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

96. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-methoxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

97. A process according to claim 78, wherein
R_1 is methyl,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-hydroxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

98. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R"' is hydrogen, R"" is phenyl,
R_8 is 4-nitro, R_8' is 4-amino,
R_9 and R_{10} are both hydrogen and
X is oxygen.

99. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-methoxy,
R_9 is 4-methoxy, R_{10} is 5-methoxy and
X is oxygen.

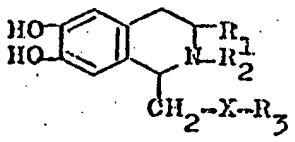
100. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both hydrogen,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-phenyl,
R_9 and R_{10} are both hydrogen and
X is oxygen.

101. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-phenoxy,
R_9 and R_{10} are both hydrogen and
X is oxygen.

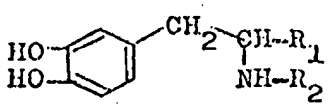
102. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 4-dimethylamino,
R_9 and R_{10} are both hydrogen and
X is sulfur.

103. A process according to claim 78, wherein
R_1 is hydrogen,
R' and R" are both benzyl,
R"' is hydrogen, R"" is phenyl,
R_8 and R_8' are both 3-methoxy,
R_9 is 4-methoxy, R_{10} is hydrogen and
X is oxygen.

104. A process according to claim 6 for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 and R_2 are each hydrogen or methyl, R_3 is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of hydroxy, chlorine, fluorine, trifluoromethyl, nitro, amino, dimethylamino, methanesulfonamido, methoxy, methylenedioxy, phenoxy, benzyloxy and phenyl, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



wherein R_1 and R_2 are each as defined above, or its salt with a malonaldehyde-acid derivative of the formula:

$$R_3\text{-}X\text{-}Y'\text{-}Z'$$

wherein R_3 and X are each as defined above, Y' is formylmethylene and Z' is ethoxycarbonyl, and if necessary, converting the resultant into its acid salt by treating it with a pharmaceutically acceptable acid.

105. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-chlorophenyl.

106. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-chlorophenyl.

107. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-methoxyphenyl.

108. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-chlorophenyl.

109. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 2-chlorophenyl.

110. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-fluorophenyl.

111. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 2-fluorophenyl.

112. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-fluorophenyl.

113. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2-hydroxyphenyl.

114. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-hydroxyphenyl.

115. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-hydroxyphenyl.

116. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-hydroxyphenyl.

117. A process according to claim 104, wherein
R_1 is methyl,
R_2 is hydrogen,
X is oxygen and
R_3 is 4-hydroxyphenyl.

118. A process according to claim 104, wherein
R_1 is hydrogen,
R_2 is methyl,
X is oxygen and
R_3 is 4-hydroxyphenyl.

119. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-methoxyphenyl.

120. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-trifluoromethylphenyl.

121. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-nitrophenyl.

122. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-aminophenyl.

123. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2,6-dimethoxyphenyl.

124. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2-chloro-4-methoxyphenyl.

125. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-dichlorophenyl.

126. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4,5-trimethoxyphenyl.

127. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 3,4,5-trimethoxyphenyl.

128. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-methylenedioxyphenyl.

129. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-benzyloxyphenyl.

130. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-biphenylyl.

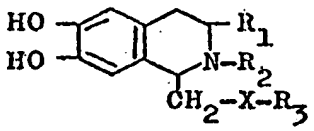
131. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-phenoxyphenyl.

132. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-dimethylaminophenyl.

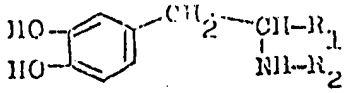
133. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-dimethoxyphenyl.

134. A process according to claim 104, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-methanesulfonamidophenyl.

135. A process according to claim 7 for preparing 1,2,3,4-tetrahydroisoquinolines of the formula:



wherein R_1 and R_2 are each hydrogen or methyl, R_3 is phenyl group which is substituted with 1 to 3 group(s) selected from a group consisting of hydroxy, chlorine, fluorine, trifluoromethyl, nitro, amino, dimethylamino, methanesulfonamido, methoxy, methylenedioxy, phenoxy, benzyloxy and phenyl, and X is oxygen or sulfur, and the pharmaceutically acceptable acid salts thereof, which comprises reacting a 3,4-dihydroxyphenethylamine derivative of the formula:



wherein R_1 and R_2 are each as defined above, or its salt with a compound of the formula:

$$R_3\text{-}X\text{-}Y''$$

wherein R_3 and X are each as defined above, and Y" is 2-acetoxyvinyl, 2,2-diacetoxyethyl or 2-hydroxyiminoethyl, and if necessary , converting the resultant into its acid salts by treating it with a pharmaceutically acceptable acid.

136. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen,
R_3 is 4-chlorophenyl and
Y" is 2-acetoxyvinyl.

137. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur,
R_3 is 4-chlorophenyl and
Y" is 2,2-diacetoxyethyl.

138. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur,
R_3 is 4-chlorophenyl and
Y" is 2-hydroxyiminoethyl.

139. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen,
R_3 is 4-chlorophenyl and
Y" is 2-hydroxyiminoethyl.

140. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen,
R_3 is 4-methoxyphenyl and
Y" is 2-hydroxyiminoethyl.

141. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-chlorophenyl.

142. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 2-chlorophenyl.

143. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-fluorophenyl.

144. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 2-fluorophenyl.

145. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-fluorophenyl.

146. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2-hydroxyphenyl.

147. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-hydroxyphenyl.

148. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-hydroxyphenyl.

149. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-hydroxyphenyl.

150. A process according to claim 135, wherein
R_1 is methyl,
R_2 is hydrogen,
X is oxygen and
R_3 is 4-hydroxyphenyl.

151. A process according to claim 135, wherein
R_1 is hydrogen,
R_2 is methyl,
X is oxygen and
R_3 is 4-hydroxyphenyl.

152. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-methoxyphenyl.

153. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3-trifluoromethylphenyl.

154. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-nitrophenyl.

155. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-aminophenyl.

156. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2,6-dimethoxyphenyl.

157. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 2-chloro-4-methoxyphenyl.

158. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-dichlorophenyl.

159. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4,5-trimethoxyphenyl.

160. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 3,4,5-trimethoxyphenyl.

161. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-methylenedioxyphenyl.

162. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-benzyloxyphenyl.

163. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-biphenylyl.

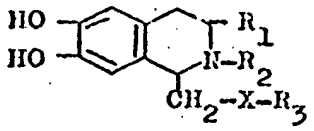
164. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-phenoxyphenyl.

165. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is sulfur and
R_3 is 4-dimethylaminophenyl.

166. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 3,4-dimethoxyphenyl.

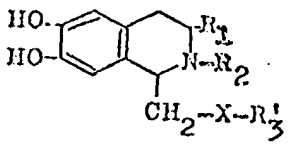
167. A process according to claim 135, wherein
R_1 and R_2 are both hydrogen atoms,
X is oxygen and
R_3 is 4-methanesulfonamidophenyl.

168. A compound of the formula:



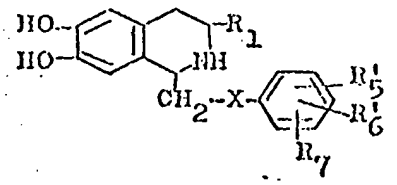
wherein R_1, R_2, R_3 and X are each as defined in claim 1 or the pharmaceutically acceptable salt thereof whenever prepared by the process of claim 1 or by an obvious chemical euivalent thereof.

169. A compound of the formula:



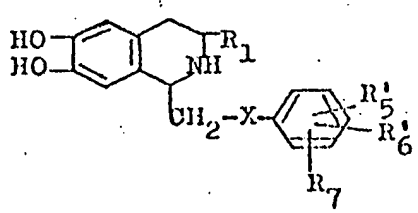
wherein R_1, R_2, R_3' and X are each as defined in claim 2 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 2 or by an obvious chemical equivalent thereof.

170. A compound of the formula:



wherein R_1, R_5', R_6', R_7 and X are each as defined in claim 3 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 3 or by an obvious chemical equivalent thereof.

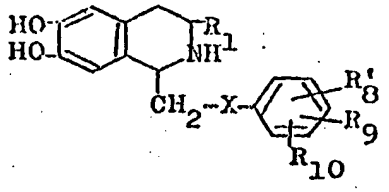
171. A compound of the formula:



wherein R_1, R_5', R_6', R_7 and X are each as defined in claim 4 or

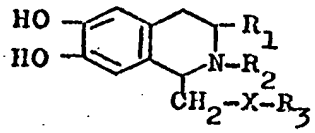
pharmaceutically acceptable salt thereof whenever prepared by the process of claim 4 or by an obvious chemical equivalent thereof.

172. A compound of the formula:



wherein R_1, R_8', R_9, R_{10} and X are each as defined in claim 5 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 5 or by an obvious chemical equivalent thereof.

173. A compound of the formula:

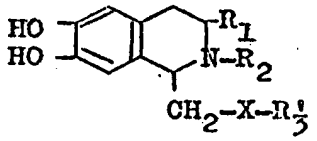


wherein R_1, R_2, R_3 and X are each as defined in claim 6 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 6 or an obvious chemical equivalent thereof.

174. A compound of the formula:

wherein R_1, R_2, R_3 and X are each as defined in claim 7 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 7 or by an obvious chemical equivalent thereof.

175. A compound of the formula:



wherein R_1, R_2, R_3' and X are each as defined in claim 8 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 8 or by an obvious chemical equivalent thereof.

176. 1-(3,4-Methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 9 or by an obvious chemical equivalent thereof.

177. 1-(4-Benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 10 or by an obvious chemical equivalent thereof.

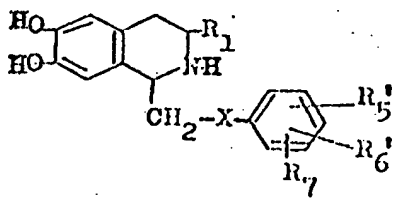
178. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 11 or by an obvious chemical equivalent thereof.

179. 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 12 or by an obvious chemical equivalent thereof.

180. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 13 or by an obvious chemical equivalent thereof.

181. 1-(4-Methanesulfonamidophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 14 or by an obvious chemical equivalent thereof.

182. A compound of the formula:



wherein R_1, R_5', R_6', R_7 and X are each as defined in claim 15 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 15 or by an obvious chemical equivalent thereof.

183. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 16 or by an obvious chemical equivalent thereof.

184. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of cliam 17 or by an obvious chemical equivalent thereof.

185. 1-(4-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 18 or by an obvious chemical equivalent thereof.

186. 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 19 or by an obvious chemical equivalent thereof.

187. 1-(2,6-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 20 or by an obvious chemical equivalent thereof.

188. 1-(3-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 21 or by an obvious chemical equivalent thereof.

189. 1-(2-Chloro-4-methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 22 or by an obvious chemical equivalent thereof.

190. 1-(3,4-Dichlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 23 or by an obvious chemical equivalent thereof.

191. 1-(4-Fluorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 24 or by an obvious chemical equivalent thereof.

192. 1-(3-Trifluoromethylphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 25 or by an obvious chemical equivalent thereof.

193. 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 26 or by an obvious chemical equivalent thereof.

194. 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 27 or by an obvious chemical equivalent thereof.

195. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 28 or by an obvious chemical equivalent thereof.

196. 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 29 or by an obvious chemical equivalent thereof.

197. 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 30 or by an obvious chemical equivalent thereof.

198. 1-(2-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 31 or by an obvious chemical equivalent thereof.

199. 1-(3-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 32 or by an obvious chemical equivalent thereof.

200. 1-(4-Hydroxyphenoxy)methyl- 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 33 or by an obvious chemical equivalent thereof.

201. 1-(4-Methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 34 or by an obvious chemical equivalent thereof.

202. 1-(4-Hydroxyphenoxy)methyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 35 or by an obvious chemical equivalent thereof.

203. 1-(4-Nitrophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 36 or by an obvious chemical equivalent thereof.

204. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 37 or by an obvious chemical equivalent thereof.

205. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 38 or by an obvious chemical equivalent thereof.

206. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 39 or by an obvious chemical equivalent thereof.

207. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 40 or by an obvious chemical equivalent thereof.

208. 1-(4-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 41 or by an obvious chemical equivalent thereof.

209. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 42 or by an obvious chemical equivalent thereof.

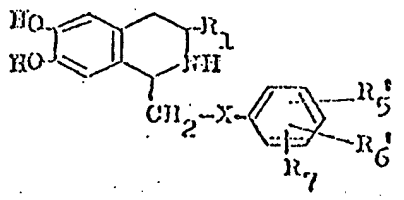
210. 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 43 or by an obvious chemical equivalent thereof.

211. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 44 or by an obvious chemical equivalent thereof.

212. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 45 or by an obvious chemical equivalent thereof.

213. 1-(3,4-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 46 or by an obvious chemical equivalent thereof.

214. A compound of the formula:



wherein R_1, R_5', R_6', R_7 and X are each as defined in claim 47 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 47 or by an obvious chemical equivalent thereof.

215. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 48 or by an obvious chemical equivalent thereof.

216. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 49 or by an obvious chemical equivalent thereof.

217. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 50 or by an obvious chemical equivalent thereof.

218. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 51 or by an obvious chemical equivalent thereof.

219. 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 52 or by an obvious chemical equivalent thereof.

220. 1-(2,6-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 53 or by an obvious chemical equivalent thereof.

221. 1-(3-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 54 or by an obvious chemical equivalent thereof.

222. 1-(2-Chloro-4-methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 55 or by an obvious chemical equivalent thereof.

223. 1-(3,4-Dichlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 56 or by an obvious chemical equivalent thereof.

224. 1-(4-Fluorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 57 or by an obvious chemical equivalent thereof.

225. 1-(3-Trifluoromethylphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 58 or by an obvious chemical equivalent thereof.

226. 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 59 or by an obvious chemical equivalent thereof.

227. 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 60 or by an obvious chemical equivalent thereof.

228. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 61 or by an obvious chemical equivalent thereof.

229. 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 62 or by an obvious chemical equivalent thereof.

230. 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 63 or by an obvious chemical equivalent thereof.

231. 1-(2-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 64 or by an obvious chemical equivalent thereof.

232. 1-(3-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 65 or by an obvious chemical equivalent thereof.

233. 1-(4-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 66 or by an obvious chemical equivalent thereof.

234. 1-(4-Methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 67 or by an obvious chemical equivalent thereof.

235. 1-(4-Hydroxyphenoxy)methyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 68 or by an obvious chemical equivalent thereof.

236. 1-(4-Nitrophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 69 or by an obvious chemical equivalent thereof.

237. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 70 or by an obvious chemical equivalent thereof.

238. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 71 or by an obvious chemical equivalent thereof.

239. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 72 or by an obvious chemical equivalent thereof.

240. 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 73 or by an obvious chemical equivalent thereof.

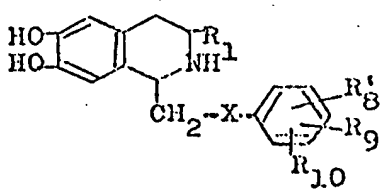
241. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 74 or by an obvious chemical equivalent thereof.

242. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 75 or by an obvious chemical equivalent thereof.

243. 1-(3,4-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 76 or by an obvious chemical equivalent thereof.

244. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 77 or by an obvious chemical equivalent thereof.

245. A compound of the formula:



wherein R_1, R_8', R_9, R_{10} and X are each as defined in claim 78 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 78 or by an obvious chemical equivalent thereof.

246. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 79 or by an obvious chemical equivalent thereof.

247. 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 80 or by an obvious chemical equivalent thereof.

248. 1-(2,6-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim81 or by an obvious chemical equivalent thereof.

249. 1-(3-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 82 or by an obvious chemical equivalent thereof.

250. 1-(2-Chloro-4-methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim83 or by an obvious chemical equivalent thereof.

251. 1-(3,4-Dichlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 84 or by an obvious chemical equivalent thereof.

252. 1-(4-Fluorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 85 or by an obvious chemical equivalent thereof.

253. 1-(3-Trifluoromethylphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 86 or by an obvious chemical equivalent thereof.

254. 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 87 or by an obvious chemical equivalent thereof.

255. 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 88 or by an obvious chemical equivalent thereof.

256. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 89 or by an obvious chemical equivalent thereof.

257. 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 90 or by an obvious chemical equivalent thereof.

258. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 91 or by an obvious chemical equivalent thereof.

259. 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 92 or by an obvious chemical equivalent thereof.

260. 1-(2-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 93 or by an obvious chemical equivalent thereof.

261. 1-(3-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 94 or by an obvious chemical equivalent thereof.

262. 1-(4-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 95 or by an obvious chemical equivalent thereof.

263. 1-(4-Methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 96 or by an obvious chemical equivalent thereof.

264. 1-(4-Hydroxyphenoxy)methyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 97 or by an obvious chemical equivalent thereof.

265. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 98 or by an obvious chemical equivalent thereof.

266. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 99 or by an obvious chemical equivalent thereof.

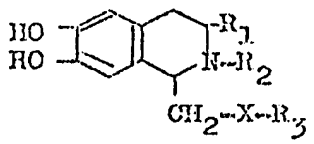
267. 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 100 or by an obvious chemical equivalent thereof.

268. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 101 or by an obvious chemical equivalent thereof.

269. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 102 or by an obvious chemical equivalent thereof.

270. 1-(3,4-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 103 or by an obvious chemical equivalent thereof.

271. A compound of the formula:



wherein R_1, R_2, R_3 and X are each as defined in claim 104 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 104 or an obvious chemical equivalent thereof.

272. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 105 or by an obvious chemical equivalent thereof.

273. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 106 or by an obvious chemical equivalent thereof.

274. 1-(4-Methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 107 or by an obvious chemical equivalent thereof.

275. 1-(3-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 108 or by an obvious chemical equivalent thereof.

276. 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 109 or by an obvious chemical equivalent thereof.

277. 1-(4-Fluorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 110 or by an obvious chemical equivalent thereof.

278. 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 111 or by an obvious chemical equivalent thereof.

279. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 112 or by an obvious chemical equivalent thereof.

280. 1-(2-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 113 or by an obvious chemical equivalent thereof.

281. 1-(3-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 114 or by an obvious chemical equivalent thereof.

282. 1-(4-Hydroxyphenoxy)methyl-6,7 dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 115 or by an obvious chemical equivalent thereof.

283. 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 116 or by an obvious chemical equivalent thereof.

284. 1-(4-Hydroxyphenoxy)methyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 117 or by an obvious chemical equivalent thereof.

285. 1-(4-Hydroxyphenoxy)methyl-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 118 or by an obvious chemical equivalent thereof.

286. 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 119 or by an obvious chemical equivalent thereof.

287. 1-(3-Trifluoromethylphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 120 or by an obvious chemical equivalent thereof.

288. 1-(4-Nitrophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 121 or by an obvious chemical equivalent thereof.

289. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 122 or by an obvious chemical equivalent thereof.

290. 1-(2,6-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 123 or by an obvious chemical equivalent thereof.

291. 1-(2-Chloro-4-methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 124 or by an obvious chemical equivalent thereof.

292. 1-(3,4-Dichlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 125 or by an obvious chemical equivalent thereof.

293. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 126 or by an obvious chemical equivalent thereof.

294. 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 127 or by an obvious chemical equivalent thereof.

295. 1-(3,4-Methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 128 or by an obvious chemical equivalent thereof.

296. 1-(4-Benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 129 or by an obvious chemical equivalent thereof.

297. 1-(4-Biphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 130 or by an obvious chemical equivalent thereof.

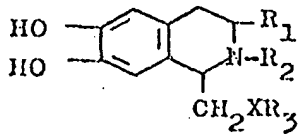
298. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 131 or by an obvious chemical equivalent thereof.

299. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 132 or by an obvious chemical equivalent thereof.

300. 1-(3,4-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 133 or by an obvious chemical equivalent thereof.

301. 1-(4-Methanesulfonamidophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 134 or by an obvious chemical equivalent thereof.

302. A compound of the formula:



wherein R_1, R_2, R_3 and X are each as defined in claim 135 or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 135 or by an obvious chemical equivalent thereof.

303. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 136 or by an obvious chemical equivalent thereof.

304. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 137 or by an obvious chemical equivalent thereof.

305. 1-(4-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 138 or by an obvious chemical equivalent thereof.

306. 1-(4-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 139 or by an obvious chemical equivalent thereof.

307. 1-(4-Methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 140 or by an obvious chemical equivalent thereof.

308. 1-(3-Chlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 141 or by an obvious chemical equivalent thereof.

309. 1-(2-Chlorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 142 or by an obvious chemical equivalent thereof.

310. 1-(4-Fluorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 143 or by an obvious chemical equivalent thereof.

311. 1-(2-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 144 or by an obvious chemical equivalent thereof.

312. 1-(4-Fluorophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 145 or by an obvious chemical equivalent thereof.

313. 1-(2-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 146 or by an obvious chemical equivalent thereof.

314. 1-(3-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 147 or by an obvious chemical equivalent thereof.

315. 1-(4-Hydroxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 148 or by an obvious chemical equivalent thereof.

316. 1-(4-Hydroxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 149 or by an obvious chemical equivalent thereof.

317. 1-(4-Hydroxyphenoxy)methyl-3-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 150 or by an obvious chemical equivalent thereof.

318. 1-(4-Hydroxyphenoxy)methyl-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 151 or by an obvious chemical equivalent thereof.

319. 1-(4-Methoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 152 or by an obvious chemical equivalent thereof.

320. 1-(3-Trifluoromethylphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 153 or by an obvious chemical equivalent thereof.

321. 1-(4-Nitrophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 154 or by an obvious chemical equivalent thereof.

322. 1-(4-Aminophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 155 or by an obvious chemical equivalent thereof.

323. 1-(2,6-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 156 or by an obvious chemical equivalent thereof.

324. 1-(2-Chloro-4-methoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 157 or by an obvious chemical equivalent thereof.

325. 1-(3,4-Dichlorophenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 158 or by an obvious chemical equivalent thereof.

326. 1-(3,4,5-Trimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 159 or by an obvious chemical equivalent thereof.

327. 1-(3,4,5-Trimethoxyphenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 160 or by an obvious chemical equivalent thereof.

328. 1-(3,4-Methylenedioxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 161 or by an obvious chemical equivalent thereof.

329. 1-(4-Benzyloxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 162 or by an obvious chemical equivalent thereof.

330. 1-(4-Diphenylyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 163 or by an obvious chemical equivalent thereof.

331. 1-(4-Phenoxyphenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 164 or by an obvious chemical equivalent thereof.

332. 1-(4-Dimethylaminophenyl)thiomethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 165 or by an obvious chemical equivalent thereof.

333. 1-(3,4-Dimethoxyphenoxy)methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 166 or by an obvious chemical equivalent thereof.

334. 1-(4-Methanesulfonamidophenyl)oxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or pharmaceutically acceptable salt thereof whenever prepared by the process of claim 167 or by an obvious chemical equivalent thereof.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente